UNIVERSAL
LIBRARY

ASYMMETRIC SYNTHESIS

AND

ASYMMETRIC INDUCTION

ST. ANDREWS UNIVERSITY PUBLICATION
No. XXXVI

ASYMMETRIC SYNTHESIS AND ASYMMETRIC INDUCTION

BY
PATRICK D. RITCHIE
B.SC., PH.D.

BASED ON A THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY PRESENTED TO THE UNIVERSITY OF ST. ANDREWS IN MARCH 1932

Published for St. Andrews University by
HUMPHREY MILFORD
OXFORD UNIVERSITY PRESS
LONDON EDINBURGH GLASGOW LEIPZIG
NEW YORK TORONTO MELBOURNE CAPE TOWN
BOMBAY CALCUTTA MADRAS SHANGHAI
1933

Printed in Great Britain by R. & R. Clark, Limited, *Edinburgh.*

ACKNOWLEDGMENT

Due acknowledgment of financial assistance in the publication of this volume is made to the University of St. Andrews

AUTHOR'S PREFACE

ALTHOUGH the existing literature on asymmetric synthesis is fairly extensive, it is for the most part confined to short and isolated publications in the various scientific journals. No really comprehensive account of the problem in all its phases appears to have been published: and the literature on the allied problem of asymmetric induction is even more scanty.

It is hoped that the present monograph will serve to fill this gap. It is based on a thesis for the degree of Doctor of Philosophy, submitted by the writer to the University of St. Andrews in March 1932. The treatment of certain sections has been modified, and a good many recent results incorporated. Essentially, however, the scheme remains the same, with the omission of the experimental details recorded in the thesis.

The writer's very grateful thanks are due to Professor Alex. McKenzie, F.R.S., for many helpful and stimulating criticisms, and to Dr. Robert Roger for invaluable help in the work on rotatory dispersion.

P. D. R.

SALTCOATS, *October* 1933

CONTENTS

PART I

ASYMMETRIC SYNTHESIS

PART II

ASYMMETRIC INDUCTION

PART I

ASYMMETRIC SYNTHESIS

I

ASYMMETRIC SYNTHESIS

A General Survey

THE phenomenal growth of synthetic organic chemistry during the twentieth century has led to the preparation, under laboratory conditions, of a large number of the less complex plant and animal products. The apparent gulf between synthetic processes occurring in the living cell and similar reactions carried out *in vitro* has thus gradually decreased: and it has become apparent that even the most complicated processes of plant and animal metabolism are controlled by orthodox physical and chemical laws. But one highly significant difference still exists between vital syntheses and their laboratory counterparts, which can hardly be too strongly emphasised. When a substance whose molecule displays only axial symmetry is produced by vital synthesis in a living cell, it is practically always found that one of the two possible antipodal forms predominates over the other, either partially or entirely, in the resulting product. In other words, such a product of natural synthesis almost invariably exhibits optical activity: whereas, if we synthesise the same compound in the laboratory, under ordinary reaction conditions, the resulting product is invariably optically inactive—that is to say, the two possible enantiomorphs are produced in exactly equal quantities. In all such syntheses, the starting-

point is a symmetrical compound, which affords two identical points of attack, equidistant from the plane of molecular symmetry, for any reagent by means of which an asymmetric carbon atom can be produced. Under normal reaction conditions, therefore, which are of a high order of symmetry, the ratio of the two enantiomorphs will, in the mass, approximate to unity: and the product will exhibit no optical activity.

Countless examples could be quoted where a product of vital synthesis is found in the living cell in a state of optical purity. (+)-Glucose * and (−)-fructose, for example, seem always to occur in plants unaccompanied by their optical antipodes [1]. The majority of the natural amino acids are lævorotatory: the bile acids, on the other hand, are dextrorotatory. (−)-Malic acid and (−)-menthol are well-known plant products, whereas (+)-malic acid and (+)-menthol do not occur in nature, and might be described as "chemical rarities".

Certain compounds, however, occur naturally in their (+)-, (−)-, and *r*-modifications. (+)-Borneol, for example, occurs in the juices of *Dryobalanops camphora*: (−)-borneol is found in *Blumea balsamifera*, and in valerian oil, which also contains *r*-borneol [2]. Similarly, (−)-piperitone is found in many of the eucalypts, while the (+)- variety has been isolated from the oil of *Andropogon Jwarancusa* and the *r*-variety from Japanese peppermint oil, and from *Cymbopogon sennaarensis*. All three forms of pinene, too, are found in nature: and the (+)- and

* Throughout this monograph, the symbols (+)- and (−)- are used to designate, respectively, dextro- and lævorotatory compounds, without any reference to configuration.

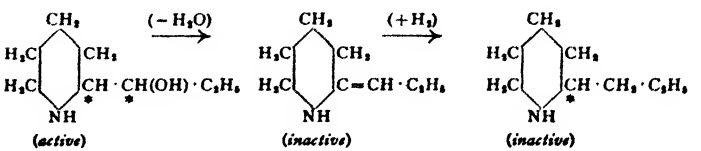
(−)-forms have even been isolated from different parts of the same plant.

The occurrence in nature of the above externally compensated substances appears, at first sight, to furnish an exception to the general rule: and another apparent anomaly lies in the formation of inactive lactic acid by the fermentation of (+)-glucose by yeast, or yeast juice. Here, however, the anomaly is more apparent than real: for (+)-glucose first yields methyl glyoxal, by a vital enzymic process, and this latter then yields inactive lactic acid by a reaction of the Cannizzaro type—*not* an enzymic process.

$$\underset{(active)}{(+)\text{-Glucose}} \longrightarrow \underset{(inactive)}{CH_3 \cdot CO \cdot CHO} \xrightarrow{(+H_2O)} \underset{(inactive)}{CH_3 \cdot CH(OH) \cdot COOH}$$

It would appear, also, that the occurrence of racemoids in living tissues is, in certain of the few known cases, due to an abnormal pathological condition [3].

In an interesting paper, Hess and Weltzien [4] have developed the view that there is a fundamentally different mode of action between plant and animal organisms. Normal products of animal metabolism occur in one antipodal form only: in plants, on the other hand, both enantiomorphs are sometimes produced simultaneously. The occurrence of, say, inactive coniine in *Conium maculatum* could be explained on the same lines as that of inactive lactic acid, quoted above, thus:

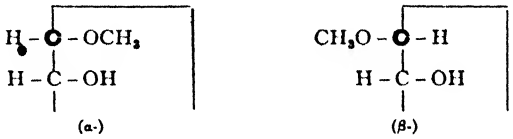


The isolation of inactive atropine from *Atropa belladonna*, too, can be explained by the ready racemisation of (−)-hyoscyamine by dilute alkali. But in the case of, say, scopoline, the inactivity cannot be attributed to any such causes: and Hess and Weltzien drew the conclusion that there is a fundamental difference between plant and animal metabolism.*

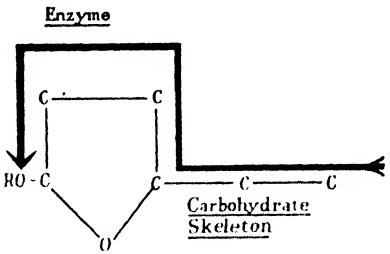
The formation of many natural optically active products is apparently synthetic: but living organisms can bring about similar results by obviously analytical methods. Thus, in Pasteur's classical biochemical experiments, it was found that the mould *Penicillium glaucum*, growing in a culture medium of racemic acid, selected for nutriment only the (+)-antipode, thus imparting a lævorotation to the medium remaining unattacked[7]. It was supposed at the time that the mould was unable to assimilate (−)-tartaric acid, but later investigations suggest that it ultimately destroys both antipodes, at very different rates, and probably in different ways. Analogous to this is the selective fermentation of sugars by sucroclastic enzymes. Thus, yeast ferments (+)-glucose, but not (−)-glucose: and similar results are observed when we consider the enzymic hydrolysis of glucosides, by α- and β-glucosidases, of which two classes maltase and emulsin, respectively, are typical. Fischer, for example, found that α-methyl glucoside is hydrolysed by maltase, but not by emulsin: whereas, with β-methyl glucoside, the reverse is the case[8]. This indicates that the

* It must be pointed out, however, that following a criticism by Pringsheim [5] Hess admitted that his suggestion was possibly rather too general [6].

hydrolysing powers of these enzymes bear the very closest relationship to the configuration of the carbohydrate molecules, which in the above cases differs at the carbon atom **C** which bears the methoxy group:



Fischer inclined to the view that the stereospecificity of such enzymic reactions is absolute: he based his famous "lock-and-key" simile on the idea that each enzyme attacks only one definite sugar configuration. The unsymmetrical enzyme molecule, which presumably forms some sort of intermediate complex with its substrate, must "fit" the glucoside molecule at every point along the chain of carbon atoms, thus:



It seems, however, nearer the truth to suppose that all types of asymmetric enzyme reactions are not *absolutely* stereo-specific, but that in certain classes at least the rate of attack of the enzyme upon the two stereoisomerides differs very markedly. Pfeffer[9] claimed to have shown that preferential assimilations by moulds and bacteria were only relative, and not absolute: and McKenzie and

Harden [10], using only a few *pure* cultures in conjunction with a variety of substrates, found that this relative specificity is unsuitable for complete optical resolution. It is very probable that an asymmetrically constituted enzyme forms intermediate additive complexes with both optical isomers in the substrate, and that these then undergo decomposition at different rates, just as in the case of the diastereoisomeric esters investigated by Marckwald and McKenzie [11] (see p. 19). Whatever may be the mechanism, such reactions emphasise once more the one-sided nature of vital processes.

We appear, then, to be dealing with a fundamental difference between "dead" and "living" matter. In laboratory syntheses, we employ highly symmetrical chemical forces: and the failure to favour one antipode at the expense of the other in such reactions is only to be expected. In the living cell, on the other hand, we appear to be dealing with a dissymmetrical force, which imparts to vital syntheses in general a one-sided bias: and for many years this force was regarded as something inherent in living matter—a "vital force", not very precisely defined, which was the prerogative of life itself, and could in no circumstances be imitated *in vitro*. Pasteur himself, to begin with, laid very great stress on this difference: and in 1860 we find him writing:

> Les produits artificiels n'ont donc aucune dissymétrie moléculaire: et je ne saurais indiquer l'existence d'une séparation plus profonde entre les produits nés sous l'influence de la vie, et tous les autres. . . .

Later, however, he modified his views somewhat. In 1884 [12], he clearly expressed the view that there was no *absolute* barrier between laboratory and vital

syntheses—that the failure to synthesise single asymmetric compounds in the laboratory might conceivably be due merely to a temporary disability, which the progress of science might eventually remove—and that the barrier might be removed by employing forces of dissymmetry not previously used in laboratory practice. Van 't Hoff, too, envisaged the possibility that an unsymmetrical physical force, not in itself the prerogative of life, might be utilised to effect such a synthesis. But for many years the gap between the two types of phenomena was not definitely bridged: and a strong "Vitalist" school of thought existed which held that it never would be.

Attention may here be directed to Professor F. R. Japp's address to the British Association in 1898, on the subject of "Stereochemistry and Vitalism" —a highly suggestive and closely reasoned statement of the problem as conceived at that date [13]. It is scarcely fair to quote isolated passages from such a logical sequence; and the reader is advised to refer to the original paper and to the controversy which it aroused [14]. An indication may be given here, however, of the views expressed. The author inclined to the view that "the production of single asymmetric molecules, or their isolation from the mixture of their enantiomorphs, is, as Pasteur firmly held, the prerogative of life. Only the living organ with its asymmetric tissues, or the asymmetric products of the living organism, or the living organism with its conception of asymmetry, can produce this result. Only asymmetry can beget asymmetry." He was strongly of the opinion that the purely accidental production of the first optically active compound—the parent substance whose asymmetry was

propagated by vital syntheses to all subsequently formed optically active natural products—could on no account have occurred, by a purely chemical coincidence. Further, even if we assume with Pasteur that certain physical forces, such as circularly polarised light, might possibly impart a bias to selected syntheses, the author suggested that "the process would not be free from the intervention of life. Such a force would necessarily be capable of acting in two opposite asymmetric senses: left to itself, it would act impartially in either sense. . . . Only the free choice of the living operator could direct it consistently into one of its two possible channels. . . . I see no escape from the conclusion that, at the moment when life first arose, a directive force came into play—a force of precisely the same character as that which enables the intelligent operator, by the exercise of his Will, to select one crystallised enantiomorph and reject its asymmetric opposite. . . ."

This view was doubtless justified at the time when the words were first written: and even when undoubted examples of asymmetric synthesis had been effected *in vitro*, as will shortly be described, a directing influence was always employed which took the form of an optically active compound previously produced by the agency of living cells. But the present writer submits that the above objections do not apply to the recent work of Kuhn and Braun [15], Kuhn and Knopf,[16] and Mitchell [17], described on pp. 50–52. Here, the experimental conditions were all such as might quite conceivably be duplicated in nature: and although the two forms of circularly polarised light employed to direct the

synthesis were, admittedly, separated by a "living operator, whose intellect embraces the conception of opposite forms of asymmetry" (*Japp*), it would appear to be an established fact that such a separation is continually occurring to a small but definite extent under natural conditions. It now seems to be well established, therefore, that asymmetric synthesis is no longer to be regarded as the prerogative of life.

The attempt to show that asymmetric vital syntheses could be explained on orthodox physical and chemical grounds, without introducing the hypothesis of a "*Vital Force*", was made by many investigators. Two phases of the problem must be distinguished. In the first place, there is the attempt to effect what has been described [18] as a "*partial asymmetric synthesis*"—that is, the positive demonstration that a new asymmetric centre can be formed in a one-sided manner when some previously formed optically active substance takes part in the reaction, to act as a directing influence. Such syntheses have been effected in two distinct ways—first, by the use of compounds of known constitution (such as (−)-menthol, (−)-borneol, and brucine), and second, by the use of complex substances of unknown constitution (such as various enzymes).

Next, following logically from this, we have the attempt to carry out the synthesis of an optically active substance by purely physical asymmetric directing forces, without the intervention of an optically active chemical compound to supply the necessary bias. Such a synthesis has been termed by various authors [19] a "*total* (*or absolute*) *asymmetric synthesis*": and we will now review in turn the work carried out on these two phases of the problem.

II

PARTIAL ASYMMETRIC SYNTHESIS

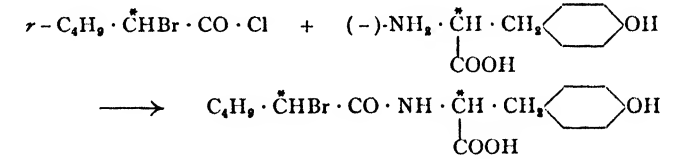
(a) *By the Agency of Optically Active Compounds of Known Constitution*

IT was Emil Fischer who first introduced the conception of asymmetric synthesis as it is understood to-day [20]. To quote his own example, consider the synthesis of (+)-glucose in the leaf-cells of green plants. Carbon dioxide and water are assumed to condense to formaldehyde under the influence of sunlight: and further condensation of formaldehyde to carbohydrates is directed by the optically active substances in the chlorophyll grains, already present in the cells, in such a manner that each successive asymmetric carbon atom in the chain, as it is formed, is produced with an excess of one of its possible antipodal forms over the other. At the end of the process, therefore, an optically active sugar is produced, the chlorophyll (which has probably been acting as a loose additive complex) being regenerated.*

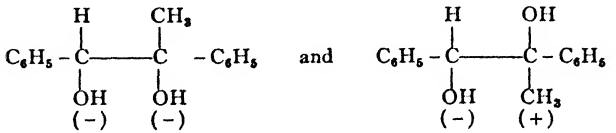
* Fischer was apparently not of the opinion that this process, which may be termed "*selective production*", was the only possible explanation. The idea of "*selective consumption*" was also in his mind: for in his lecture to the German Chemical Society in 1890 on "Synthesis in the Sugar Group", he says: "No fact hitherto known speaks against the view that the plant, like chemical synthesis, first prepares the inactive sugars: that it then resolves them into their active constituents, using the members of the *d*-mannitol series in building up starch, cellulose, inulin, etc., whilst the optical isomerides serve for other purposes, at present unknown to us". It will be seen from the following pages that selective production and consumption are both very probably involved in vital syntheses.

That one-sided reactions of the above type may occur is proved by Fischer's work on the cyanohydrin reaction, whereby a new asymmetric carbon atom is produced at the end of a carbohydrate chain, two new isomers (designated the *α*- and *β*-forms) therefore being theoretically possible. For example, in the synthesis of gluco-octonic acid, the *α*-form was found to predominate over the *β*-form: and in the similar synthesis of manno-heptonic acid, 87 per cent of the theoretical yield was composed of the *α*-form, while the *β*-form was not isolated at all [21]. It must, however, be emphasised that Fischer himself never regarded these syntheses of sugars as examples of asymmetric synthesis in the sense of the term devised by himself.

Somewhat analogous results have been obtained in various other cases. Fischer [22], for example, found that the action of *r*-*α*-bromo-*iso*-capronyl chloride upon (−)-tyrosine appeared to yield only one * of the two possible diastereoisomerides:

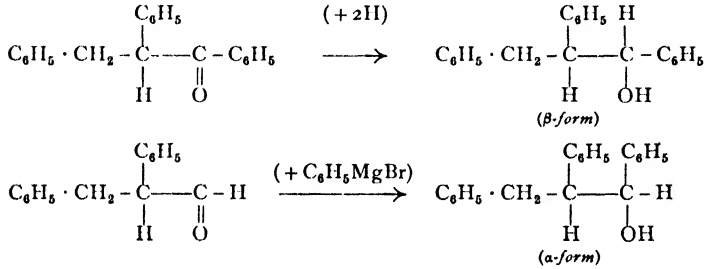


Similarly, McKenzie and Wren [23] obtained only one of the two theoretically possible glycols:

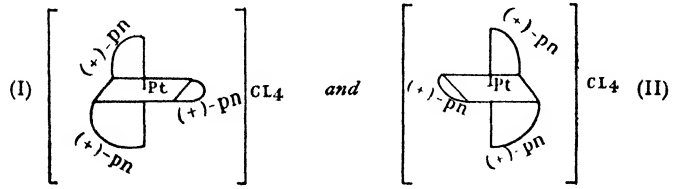


* The possibility is not excluded, however, that the apparently homogeneous product consisted of mixed crystals of the two forms.

by the action of methyl magnesium iodide upon (−)-benzoin. Other similar results have been recorded in the field of glycol synthesis, only one of two possible diastereoisomerides being formed. It has, in some cases, however, been found possible to synthesise the missing isomer by inverting the order in which the atoms or radicals attached to the new asymmetric centre are introduced into the molecule[24]. For example:



Analogous results, which have sometimes been erroneously designated as "partial asymmetric syntheses", have been obtained in the case of certain optically active coordination compounds. Smirnov[25], for example, obtained only one of the two possible complex salts (I and II) from platinic chloride and (+)-propylenediamine ("(+)-pn").



In a similar way, Jaeger and Blumendal[26] examined the reaction between *r-trans*-1 : 2-*cyclo*-pentylenediamine ("Cpt") and salts of rhodium or

cobalt, and obtained only two of the four possible salts:

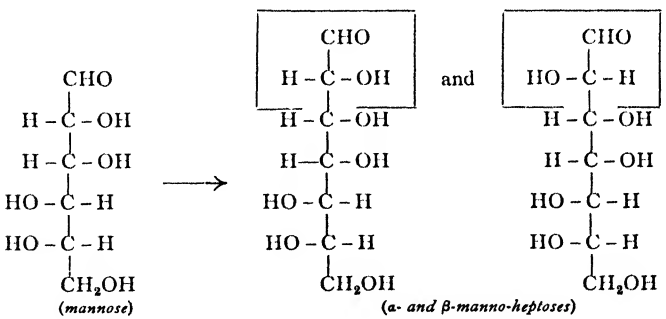
$$(+)\text{-}[M\{(-)\text{-}Cpt\}_3]X_3 \quad \textit{and} \quad (-)\text{-}[M\{(+)\text{-}Cpt\}_3]X_3$$
$$\textit{not}\ (+)\text{-}[M\{(+)\text{-}Cpt\}_3]X_3 \quad \textit{and} \quad (-)\text{-}[M\{(-)\text{-}Cpt\}_3]X_3$$

Lifschitz [27] describes other cases of a similar type; while reference to earlier papers by Tschugaeff [28] will disclose still more.

Reactions of this type, though definitely unsymmetrical, are not, however, to be regarded as examples of asymmetric synthesis according to Fischer's conception; and the phrase "partial asymmetric synthesis" is best reserved for cases of the type described in the following pages.

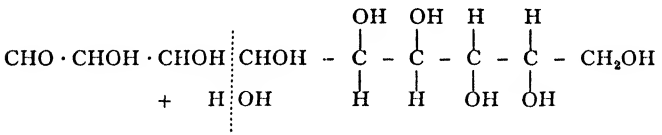
From consideration of reactions such as the above, Fischer argued that an asymmetric synthesis could theoretically be effected on the following lines:

Mannose, by the cyanohydrin reaction, can theoretically yield an *α*- and a *β*-manno-heptose, thus:

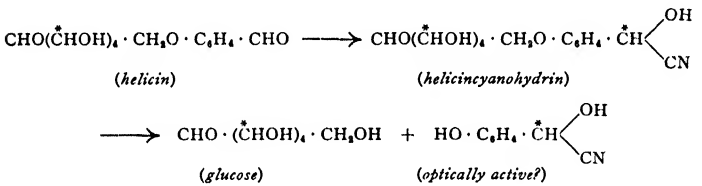


In practice, only one isomer is formed: and in a similar way, only one manno-octose is formed from this synthetic manno-heptose, and only one manno-nonose from the manno-octose. If we could

disrupt the final synthetic manno-nonose in the particular manner represented below, it should be possible, theoretically, to get back to the original mannose molecule, with the elimination of a molecule of optically active glyceric aldehyde, $CHO \cdot \overset{*}{C}H(OH) \cdot CH_2OH$:



Thus, Fischer [29] attempted to prepare optically active salicylaldehydecyanohydrin from helicin, in the following way:



The desired product could not, however, be isolated. Subsequently, a modified synthesis on these lines was carried out by Fischer and Slimmer [30]. Starting from tetra-acetyl helicin, *o*-hydroxy-mandelic acid was obtained by the cyanohydrin reaction: and by the action of zinc diethyl on the same glucoside, *o*-hydroxy-phenyl-ethyl-carbinol was isolated. Both products were apparently in an optically active condition. Further work, however, tended to show that these apparently positive results were due to the presence of a strongly optically active condensation product of the glucoside: and the work had to be abandoned owing to technical difficulties.

Other unsuccessful attacks were also made upon

the problem about this time. Cohen and Whiteley [31] reduced the (−)-menthyl esters of mesaconic, phenylcrotonic, and pyruvic acids, and also carried out the bromination of (−)-menthyl and (−)-amyl cinnamates: but, although saturation of the double bond had generated a new asymmetric carbon atom in each case, no optical activity was detected in the acids obtained after removal of the (−)-menthol.

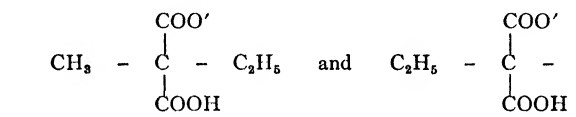
In a similar way, Kipping [32] reduced quinine pyruvate and lævulinate, and (−)-bornyl benzoylformate and pyruvate, as well as the oxime of the last-named ester: but again the results were negative. It is possible that an asymmetric synthesis may actually have been effected in some of the above cases, and inadvertently overlooked. Cohen and Whiteley, for example, did not examine the activity of the lactic acid formed from the pyruvate until *after* crystallisation of its zinc salt, whereby any excess of optically active acid that might have been produced would have been overlooked, in the mother liquors.

Hartwall [33] also suggested the reduction of menthyl (or bornyl) citraconates and mesaconates: but no experiments in this direction are recorded by him.

In 1904, Marckwald [34] claimed to have obtained the first positive result. His starting-point was methyl-ethyl-malonic acid, the molecule of which becomes unsymmetrical on neutralising *one* carboxyl group with a base. In this case, the base chosen was brucine: the solution of the acid brucine salt was evaporated, and the solid which separated was removed and heated to 170°, thereby eliminating carbon dioxide from the uncombined carboxyl group, and forming the brucine salt of valeric

(methyl-ethyl-acetic) acid. On removal of brucine, the resulting acid was found to contain 55 per cent of the (−)-antipode and 45 per cent of the (+)-antipode. Subsequently, Tijmstra, Bz.,[35] modified Marckwald's experimental conditions, and obtained a rather more strongly lævorotatory product.

This result has been somewhat severely criticised. Cohen and Patterson[36] do not consider this to be an asymmetric synthesis, since they regard a solution of methyl-ethyl-malonic acid as containing the enantiomorphous ions:



Hence, the acid in solution already contains an asymmetric carbon atom, even before combination with brucine. Marckwald[37] replied that the salt may be produced in non-ionising-solvents, such as ether or chloroform, with the same results: and at the same time, he gave his precise and much-quoted definition of an asymmetric synthesis:

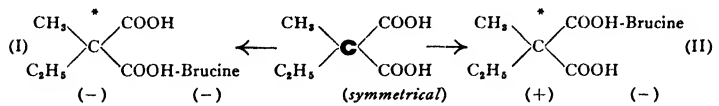
> Asymmetrische Synthesen sind solche, welche aus symmetrisch konstituierten Verbindungen unter intermediärer Benutzung optischaktiver Stoffe, aber unter Vermeidung jedes analytischen Vorganges, optisch-aktive Substanzen erzeugen. . . .

Cohen and Patterson further contend, and with some justice, that analytical separation, of Pasteur's second (alkaloidal) type, had been effected in the first stage of Marckwald's synthesis; but it should be noted that ten years later, Erlenmeyer, Jun.,[38] confirmed Marckwald's result by expelling the solvent *entirely* from an alcoholic solution of brucine

and methyl-ethyl-malonic acid in equivalent amounts, and subsequently heating. Here, no analytical separation of fractions of the brucine salt could have taken place.

The question is, perhaps, best approached from the standpoint of Marckwald and McKenzie's work on the esterification of *r*-mandelic acid and (−)-menthol [11]. It was found by these investigators that (−)-menthyl-(+)-mandelate was formed at a greater rate than (−)-menthyl-(−)-mandelate, in the above esterification. If, therefore, the reaction was interrupted before the mandelic acid was *completely* esterified, or if the *r*-acid was originally present in excess over the (−)-menthol, an excess of the (−)-antipode was left in the portion of acid remaining uncombined. If, on the other hand, the experimental conditions were such that the acid was *completely* esterified, the final product consisted of *equal* amounts of the two diastereoisomeric esters, though they were formed with different reaction velocities. The principle underlying these striking results is perfectly general, and applies to the rate of decomposition of diastereoisomerides as well as their rate of formation.

Applying these conceptions to Marckwald's valeric acid synthesis, we see that it is only *after* combination of the symmetrical acid molecule with brucine has occurred that the carbon atom **C** is asymmetric.



Hence, we are not dealing in this experiment with the combination of an active base and a racemic

acid: and the diastereoisomerides I and II should, presumably, be formed in equal quantity. If, now, we eliminate carbon dioxide from the equimolecular mixture of I and II, the two diastereoisomerides would be expected to decompose with different reaction velocities. But, if the decomposition be carried to *completion*, and not stopped before the more slowly decomposing isomer has given off all its carbon dioxide, the final product will contain *equal* quantities of brucine-(−)-valerate and brucine-(+)-valerate, yielding inactive valeric acid on decomposition. In this case, obviously, no asymmetric synthesis has been effected.

The fact that Marckwald actually obtained an optically active product may therefore be explained in two ways:

(i) The decomposition of the mixture of I and II may have been stopped before *complete* elimination of carbon dioxide had occurred, in which case the activity was presumably due to a reaction analogous to that described by Marckwald and McKenzie—not to an asymmetric synthesis.*

(ii) On the other hand, the optical activity of the product may have been due to the initial formation of I and II in *unequal* amounts, followed by *complete* elimination of carbon dioxide from both diastereoisomerides, in

* Marckwald's definition of asymmetric synthesis, though precise, has not been recognised, or has, possibly, been misinterpreted, by various authors, who use the term somewhat loosely, and not in the sense of the definition [39]. The fractional esterifications and saponifications of stereoisomerides investigated by Marckwald and McKenzie are not regarded by these authors as providing examples of asymmetric synthesis.

which case an asymmetric synthesis had really been effected.

But the quoted experimental details are insufficient to let us say to which cause the final result was due: and hence, in the opinion of the present writer, we cannot definitely attribute the first true asymmetric synthesis to Marckwald. Indeed, if it were not for Erlenmeyer's repetition of the experiment, one would be inclined to say that Marckwald's result was due to incomplete elimination of carbon dioxide, or to an analytical separation or resolution: for, since the carbon atom **C** is not asymmetric until combination of acid and base has actually produced a molecule of either I or II, there seems to be no very obvious reason for the formation of these substances in unequal amounts.

Immediately after the publication of Marckwald's result, McKenzie [40] independently reported the first of a long series of undoubted asymmetric syntheses, to which none of the above objections can be raised. The reduction of optically active *a*-ketonic esters (previously attempted by Cohen and Whiteley, and by Kipping) was carried out by treatment of their ethereal solutions with aluminium amalgam. A first attempt to obtain optically active mandelic acid on the following lines—

$$C_6H_5 \cdot CO \cdot COOC_{10}H_{19} \xrightarrow[(-)]{} C_6H_5 \cdot \overset{*}{C}H(OH) \cdot COOC_{10}H_{19} \xrightarrow[(-)]{} C_6H_5 \cdot \overset{*}{C}H(OH) \cdot COOH \quad (active?)$$

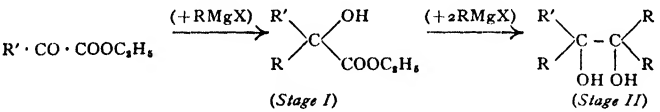
—was unsuccessful: for although an excess of (−)-menthyl-(−)-mandelate over (−)-menthyl-(+)-mandelate was produced, the alcoholic potash employed to saponify the ester mixture caused racemisation, and the resulting acid was optically

inactive [40]. Later, however [41], the expected result was achieved by acetylating the reduced ester mixture, and then saponifying, when an optically active mandelic acid was obtained: and it was also found that the pyruvates of (−)-menthol [42], (−)-borneol [44], and (−)-amyl alcohol [45] all yielded optically active lactic acid, thus:

$$\underset{(active)}{CH_3CO\cdot COO\overset{*}{R}} \longrightarrow \underset{(active)}{CH_3\overset{*}{C}H(OH)\cdot COO\overset{*}{R}} \longrightarrow \underset{(active)}{CH_3\cdot \overset{*}{C}H(OH)\cdot COOH}$$

(*where* $\overset{*}{R}$ *is an optically active grouping*)

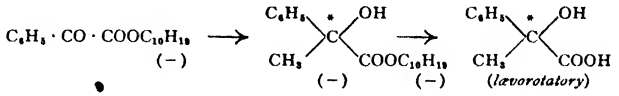
Application of an entirely different method also led to the realisation of an asymmetric synthesis. It had previously been shown by Grignard [46] that when an organo-magnesium-halide acts on the ester of an *α*-ketonic acid, the reaction proceeds in two successive stages, of which the second can be almost eliminated by judicious choice of experimental conditions:



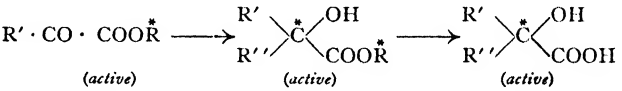
(*Stage I*) (*Stage II*)

Applying this reaction, McKenzie and his co-workers have acted on the menthyl, bornyl, amyl, and *β*-octyl esters of a variety of *α*-ketonic acids, with different Grignard reagents. The first successful synthesis of this type [40] was effected by acting upon (−)-menthyl benzoylformate with methyl magnesium iodide, conditions being chosen to limit the reaction to Stage I. The product was decomposed with ice and mineral acid, yielding a mixture of (−)-menthyl-(−)-atrolactinate and (−)-menthyl-(+)-atrolactinate, with the former in excess. Saponification with excess of potash, followed by complete

removal of (-)-menthol, led to the formation of a lævorotatory potassium salt, from which lævorotatory atrolactinic acid was obtained:



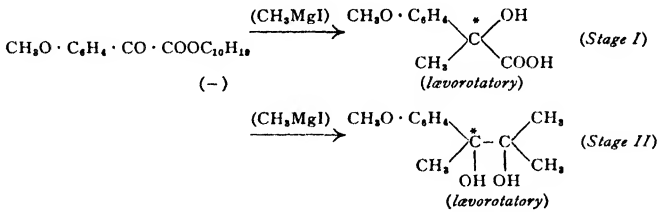
Generalising, the following type of reaction was realised in each case examined:



(*Where* R* *is an optically active grouping*)

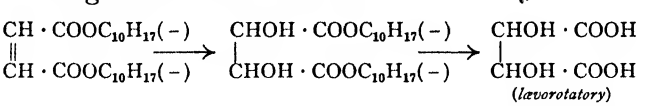
The new asymmetric carbon atom (C*) was always generated in a one-sided manner, under the directing influence of the optically active alcoholic radical (R*): and when the latter was subsequently removed by hydrolysis, an optically active substituted glycollic acid remained.

The formation of an optically active glycol (*Stage II*) has also been noted in one case [48].



Four different *a*-ketonic acids have been examined in this way—pyruvic [44, etc.], benzoylformic [40, etc.], *a*-naphthoylformic [49], and anisoylformic [47] acids. Thirty different cases of this type of asymmetric synthesis have been observed: these are tabulated on pp. 108-109, and will be considered later on in fuller detail.

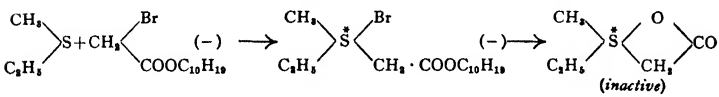
In addition, an extension of the reduction method described above enabled McKenzie and Wren [50] to effect the asymmetric synthesis of (+)- and (−)-tartaric acids. (−)-Bornyl fumarate was oxidised by potassium permanganate in acid solution: and the following scheme was realised:



More convincing results were obtained by using the (−)-menthyl ester, or the acid (−)-bornyl ester: while, as was to be expected, the oxidation of (+)-bornyl fumarate led to the asymmetric synthesis of (+)-tartaric acid.

A study of the experimental conditions in all the above results of McKenzie and his co-workers will show that none of the results can be ascribed to incomplete saponification of the optically active ester mixtures, or to the accidental action of moulds or fungi, or, in short, to anything but definite partial asymmetric synthesis.

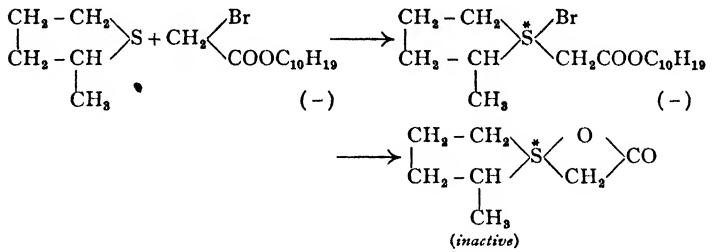
Two unsuccessful attempted asymmetric syntheses of quadrivalent sulphur are worthy of note here. Smiles [51] formed the addition compound of methyl-ethyl-sulphide and(−)-menthyl bromacetate: but saponification of the resulting ester led to the formation of an optically inactive thetine, thus:



In view of Pope's earlier results [52], this was presumably not due to a racemisation effect during saponification.

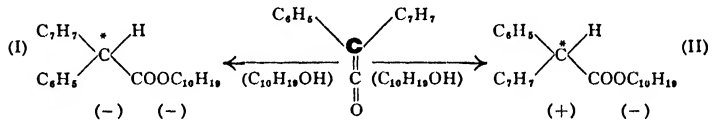
More recently, Menon and Guha [53] made a fresh

attack on this problem; but, in the following synthesis, the final thetine was once more found to be optically inactive:



A possible reason for the negative results of these syntheses is suggested on the following page.

A novel method of attacking the problem of asymmetric synthesis was adopted by Weiss [54], who studied the addition of (−)-menthol to phenyl-*p*-tolyl-keten:



Weiss isolated the resulting (−)-menthyl phenyl-*p*-tolyl-acetate, and concluded from his figures that the (−)-menthyl-(+)-ester (II) was formed in the reaction quite free from the (−)-menthyl-(−)-ester (I). He claimed, on these grounds, to have effected an asymmetric synthesis: but, according to Marckwald's very exact definition, such a synthesis would not have been complete unless Weiss had saponified his ester, and obtained an optically active sample of phenyl-*p*-tolyl-acetic acid. Actually, he isolated only the *r*-acid * on saponification, as was only to

* It has several times been erroneously stated that Weiss actually isolated the (+)-acid [55].

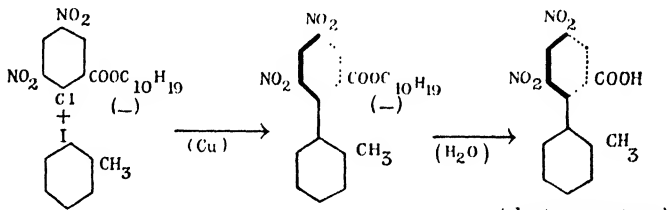
be expected, since McKenzie and Widdows [56] have shown that very ready racemisation occurs when (−)-menthyl-(+)-phenyl-*p*-tolyl-acetate is saponified by alcoholic potash. Weiss, therefore, did not effect a true asymmetric synthesis: and, in fact, the evidence upon which he based his claim to have isolated ester II, free from ester I, is somewhat unreliable. The product was obtained as a syrup, whereas McKenzie and Widdows had described the ester as a solid, m.p. 53-54°: and the quoted analysis was not very satisfactory, as regards hydrogen content. It is probable that the ester was still contaminated with some by-product of the keten reaction.

Actually, if the argument elaborated on p. 20 is valid, there is no very obvious reason why esters I and II should be formed in unequal amounts, since on classical considerations the carbon atom **C** is not asymmetric * until combination with (−)-menthol has actually occurred. This criticism is advanced only tentatively: but it also suggests a reason for the failure of the sulphur syntheses of Smiles, and of Menon and Guha, for here, also, we are not dealing with the combination of two dissymmetric molecules. The sulphur atom is not asymmetric until it has assumed the quadrivalent state and combined with a molecule of (−)-menthyl bromacetate: and we would not, therefore, expect

* It should be remembered, however, that Dunkel [57] has put forward reasons for believing that a molecule such as $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!C=C=O$ is capable of existing in optically active modifications. No experimental evidence for this statement has so far been adduced: but a definite confirmation of Weiss' claim might be taken as supplying such evidence.

a differential formation of diastereoisomerides on the lines laid down by Marckwald and McKenzie.

Up to the present, no compound has been found in nature which owes its optical activity to "molecular asymmetry"—that is, to asymmetry of the molecule as a whole, without the presence of a classical asymmetric centre [58]. It is therefore interesting to note that Lesslie and Turner [59] claim to have effected the asymmetric synthesis of a substance of this type. A mixture of (−)-menthyl 2-chloro-3 : 5-dinitrobenzoate and *o*-iodotoluene was heated with copper-bronze : the (−)-menthyl ester of 2 : 4-dinitro-2′-methyl-diphenyl-6-carboxylic acid was obtained, which on hydrolysis yielded the free acid in an optically active state, thus:

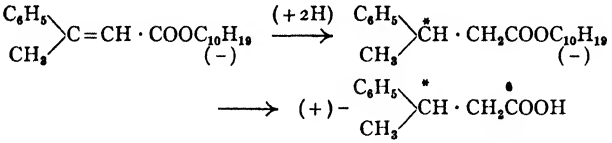


(dextrorotatory)

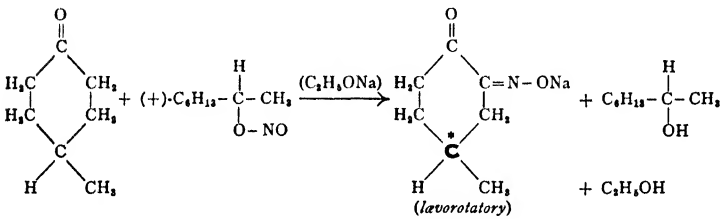
The quoted experimental details are, however, not altogether conclusive: and it is not impossible that here the final activity was due to a partial analytical separation of the diastereoisomeric esters during hydrolysis by means of acid.

In passing, it is of interest to note that Vavon and Jakubowicz [284] have recently realised an asymmetric synthesis of the type unsuccessfully attempted by Cohen and Whiteley [31]. Esters of β-methyl-cinnamic acid with six different optically active alcohols were catalytically hydrogenated in the presence of platinum black: and, after saponification and removal of

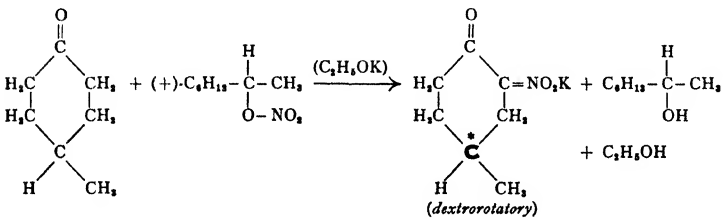
the alcohols, optically active β-phenyl-butyric acid was obtained in each case. For example, the (−)-menthyl ester gave:



Two interesting results have recently been recorded by Shriner and co-workers which may conveniently be considered at this point. The action of (+)-β-octyl nitrite on 4-methyl-*cyclo*-hexanone, in the presence of sodium ethoxide, gave rise to a lævorotatory sodium derivative of 2-oximino-4-methyl-*cyclo*-hexanone, thus [60]:



A second example of this type of synthesis has been found in the condensation of 4-methyl-*cyclo*-hexanone and (+)-β-octyl nitrate [61]:



In this second case, the activity of the potassium salt may be due to the asymmetry of the carbon atom **C***, as in the first example: but some evidence

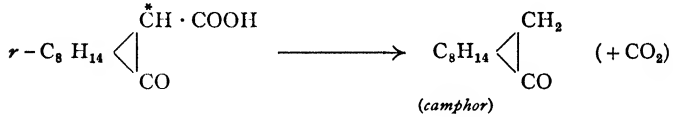
was obtained that this compound may provide a third example of optically active salts of secondary nitro-compounds, similar to those described later, on p. 100.

It is open to doubt whether these novel reactions should be termed "asymmetric syntheses" in the strict sense of Marckwald's definition, into which may be read the tacit implication that the intermediate directing agent must be regenerated in its original form. In the above cases, though the optically active β-octyl group is certainly split off from the intermediate complex, during the reaction which actually generates the new asymmetric centre, it is no longer in the form of the original ester.

It should be noted that, in all the above asymmetric syntheses, the optical activity of the product falls far short of the value for 100 per cent optical purity, where this constant is known. In other words, we are dealing in all these cases with the formation of two enantiomorphs in unequal amounts, under the influence of a pre-existing molecular dissymmetry—*not* with the exclusive formation of one enantiomorph only. It therefore becomes a matter of fundamental importance to determine whether vital asymmetric syntheses can be explained on a similar basis, or whether the totally selective production of a single enantiomorph is here involved. The fact that most naturally occurring optically active products occur in the optically pure state is not in itself sufficient to exclude the possibility that the predominating antipode is accompanied by a trace of its mirror image. Actually, it has been shown by the work of many investigators that the one-sided nature of vital syntheses is due only to the different

reaction velocities with which two enantiomorphs are synthesised (or decomposed) by some naturally occurring unsymmetrical reagent—an enzyme, for example.

In the first place, the work of Bredig and his collaborators [62] has thrown considerable light on the kinetics of catalytic elimination of carbon dioxide from carboxylic acids—a phenomenon with a particular physiological interest in view of Neuberg's work on "carboxylase". For example, carbon dioxide is readily eliminated from camphorcarboxylic acid on heating, thus:



Basic catalysts accelerate this elimination: and by employing an optically active base, such as (−)-nicotine, it was shown that the two antipodal forms of the acid decompose with different velocities, with the formation of an optically active camphor. These investigations, carried out by Bredig and Fajans [62], were later extended to bromcamphorcarboxylic acid: and from an analysis of the collected results, it was deduced that the action is truly catalytic, a transient intermediate complex of acid and basic catalyst being formed, with subsequent regeneration of the latter, and that this catalytic reaction is in every way analogous to enzyme action.

Other results of a similar nature are recorded in the literature. It was, for example, found by Wuyts [63] that phenyl-methyl-carbinol undergoes catalytic dehydration at 100° C. in the presence of 1 per cent of Reychler's (+)-camphorsulphonic acid, the two

antipodes decomposing at different rates. More recently, Wegler [64] has observed differing esterification-velocities for the optical antipodes of a racemate in the presence of optically active catalysts. Treatment of inactive phenyl-methyl-carbinol with acetic acid, acetic anhydride, or acetyl chloride, in the presence of brucine, resulted in the preferential esterification of one antipode; and a similar result was observed with phenyl-ethyl-carbinol. Further, the action of ethyl chloroformate on inactive *a*-phenylethylamine, again in presence of brucine, resulted in the formation of a (+)-urethane, the uncombined amine now showing a lævorotation.

In the second place, exactly similar differences in reaction velocity have been observed in a large number of enzymic reactions. For example, Dakin [65] found that benzyl-(−)-mandelate is hydrolysed about 40 per cent more slowly than benzyl-(+)-mandelate by the enzyme lipase: while Herzog and Meier [66] found that the "oxidases" from various moulds oxidise (+)-tartaric acid more rapidly than its enantiomorph. Many other striking examples of such differences in reaction velocity have been recorded for many moulds and enzymes—notably by McKenzie and Harden [10], Abderhalden and Pringsheim [67], Condelli [68], Neuberg, Wagner, and Jacobsohn [69], Willstätter, Kuhn, and Bamann [70], and Mitchell [71].

Finally, the parallel between selective enzyme action and that of simpler optically active catalysts such as quinidine and quinine was completed by the work of Bredig and his collaborators. The addition of hydrocyanic acid to benzaldehyde, in the presence of (+)-quinidine, or (−)-quinine, followed by

hydrolysis, was shown by Bredig and Fiske to result in the formation of (+)- and of (−)-mandelic acid, respectively [72]: and Bredig and Minaeff have recently recorded analogous results, employing five other aldehydes [73]. These reactions—true asymmetric syntheses in the sense of Marckwald's definition—are exactly parallel to Rosenthaler's experiment, described in the following section, where the same result was obtained by employing the enzyme emulsin as the catalyst [74].

More recently, Bredig and Gerstner [75] have found that cotton fibre,* on the introduction of dimethylamino groupings into its structure, has a similar asymmetric catalytic effect in this reaction, a lævorotatory mandelonitrile being produced.

One more interesting result may be mentioned in this connection. Bamann and Laeverenz [76] have linked up the results of Bredig and Fiske on optically active catalysts with those obtained in the field of asymmetric enzymic hydrolysis of esters. They demonstrated that the addition of quinine, strychnine, and other alkaloids increased the preferential hydrolysis of the (+)-antipode of inactive ethyl mandelate by rabbit "esterase".

It may be mentioned in conclusion that many complex metallic salts have recently been shown to exhibit a catalytic oxidising effect, exactly analogous to the enzymic action of oxidases: and Shibata and Tsuchida [77] have found that these salts even imitate the stereo-specificity of such enzymes. When, for

* Since Bredig and Gerstner describe their cotton fibre ("*Baumwolle*") as being "*bekannter Zusammensetzung*", their result is included in the present section: but it seems rather a sweeping statement to describe a cellulose fibre in such terms.

example, *r*-3 : 4-dihydroxy-phenyl-alanine was oxidised under the catalytic influence of (−)-chloro-ammino-di-ethylenediamine-cobaltibromide, $[Co(en_2, NH_3, Cl)]Br_2$, it was found that the (−)-amino acid was preferentially destroyed.

III

PARTIAL ASYMMETRIC SYNTHESIS

(b) *By the Agency of Optically Active Substances of Unknown Constitution*

LET us pass, now, to those partial asymmetric syntheses which have been effected by the agency of substances of unknown constitution. These have been carried out under laboratory conditions by the action of enzymes—either by the direct action of various *living* organisms, such as moulds, fungi, or bacteria, or by the action of the enzymes *in the absence of the living parent cells*. We will consider these experiments individually: and it will be seen that they all constitute true asymmetric syntheses in the sense of Marckwald's definition, the directing influence being an enzyme instead of an optically active compound of known constitution. These enzymes almost certainly act as soluble organic catalysts, most probably by adsorption and subsequent liberation, thus complying with the classical definition. Here, therefore, we are actually dealing with a series of vital asymmetric syntheses, as carried out by living cells, but under more or less controlled laboratory conditions.

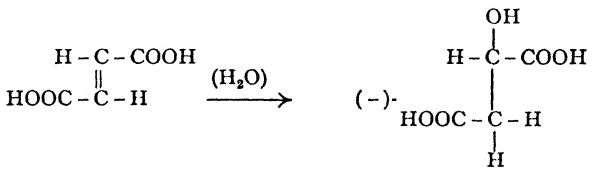
In the first place, Rosenthaler [74] has carried out the unsymmetrical addition of hydrocyanic acid to twenty-one different aldehydes in the presence of the "*oxynitrilase*" contained in almond emulsin: and in each case an optically active cyanohydrin was produced, which in certain cases was hydrolysed

to the corresponding active hydroxy-acid. Thus, a dextrorotatory mandelonitrile was obtained from benzaldehyde, apparently in large excess over its enantiomorph, since hydrolysis gave rise to (−)-mandelic acid, which was optically pure after only two crystallisations from benzene:

$$C_6H_5 \cdot CHO \longrightarrow (+)\text{-}C_6H_5 \cdot \overset{*}{C}HOH \cdot CN \longrightarrow (-)\text{-}C_6H_5 \cdot \overset{*}{C}HOH \cdot COOH$$

By using *"oxynitrilases"* from different sources, Krieble [78] was able to isolate a lævorotatory mandelonitrile. Later work by Krieble and Wieland [79] showed that by working at low temperatures, and with low pH values, the coexistent symmetrical chemical synthesis is largely suppressed, and spontaneous racemisation of the nitrile is to a great extent avoided. Using an extract of peach leaves, under the above conditions, (+)-mandelonitrile was obtained in a fairly high degree of optical purity.*

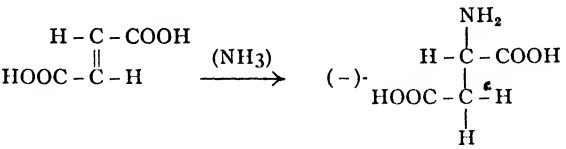
By injecting ammonium cinnamate into dog tissues, Dakin [81] succeeded in obtaining lævorotatory β-phenyl-β-hydroxy-propionic acid as a product of metabolism. Later, by means of a *"fumarase"* in muscle extract, the same worker converted fumaric acid into a lævorotatory malic acid. Challenger and Klein [82], and Jacobsohn [83], have effected similar syntheses, the latter obtaining (−)-malic acid in 80 per cent yield.



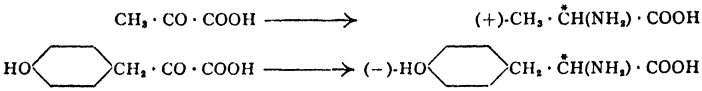
Very similar results were obtained by Sumiki [84].

* It may be noted that optically pure crystalline (+)-mandelonitrile has recently been prepared from amygdalin, by Smith [80].

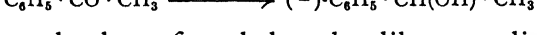
By the addition of ammonia to fumaric acid, in the presence of "*aspartase*", from beer yeast, a 76 per cent yield of (−)-aspartic acid was obtained.



It has been found, also, that perfusion of liver with certain *α*-ketonic acids gave rise to the corresponding *α*-amino acids in an optically active state [85]:



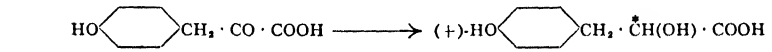
Neuberg and his co-workers have brought about a series of asymmetric phytochemical reductions, by utilising the reducing enzymes ("*reductases*") which are found in many types of living cells. In this way, six different unsymmetrical ketones were reduced in the presence of yeast and aqueous sucrose: and in each case an optically active secondary alcohol was produced [86]. For example:



It has also been found that the diketone, diacetyl, can be phytochemically reduced to acetoin, and thence to *βγ*-butylene glycol, both products being formed in an optically active state [87, 88]: while butyroin has been reduced to a mixture of (+)- and *meso*-4, 5-octandiols [89]. In a similar way, benzil has been reduced to a slightly lævorotatory benzoin, though in this case the reduction could not be carried to the next stage [78]. The work has also been extended to halogenated ketones: methyl-*α*-chloroethyl ketone

has been phytochemically reduced to (−)-β-hydroxy-chlorobutane [90], and *aa*-dichloroacetone to (−)-*aa*-dichloro-*iso*-propyl alcohol [91].

Benzoylformic acid has been reduced to (−)-mandelic acid by means of yeast, or ox-liver extract [276]: while *r*-*o*-methyl-*cyclo*-hexanone, under the influence of yeast, gave rise to the corresponding carbinol in a dextrorotatory form [277]. It may be mentioned, too, that the action of the mould *Oidium lactis* upon *p*-hydroxy-phenyl-pyruvic acid has been found to yield (+)-*p*-hydroxy-phenyl-lactic acid [278]:

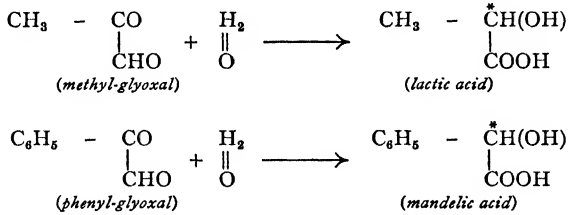


In 1921, Neuberg and Hirsch [92] recorded the existence, in yeast, of an important new enzyme, which they named "*carboligase*". It acts by linking up a molecule of the acetaldehyde produced in sugar fermentation with another aldehydic molecule—either acetaldehyde itself, or another aldehyde added intentionally to the fermenting mixture—somewhat after the fashion of the "benzoin condensation", thus:

The ketol thus produced is usually markedly optically active. Thus, the addition of benzaldehyde to a solution of sugar undergoing yeast fermentation gave rise to an optically active ketol [92], which has been formulated by some workers as $CH_3 \cdot CHOH \cdot CO \cdot C_6H_5$, and by others as $C_6H_5 \cdot CHOH \cdot CO \cdot CH_3$. The latter formula has been most generally favoured [93]: but the particular constitution adopted does not, of course, affect the remarkable stereochemical significance of carboli-

gatic syntheses [94]. Similar reactions have been effected by adding *o*-chlorobenzaldehyde [95] and *o*- and *p*-tolualdehydes [96] to the fermenting solution, an optically active ketol being produced in each case. In cases where no second aldehyde is added to the mixture, optically active acetoin is usually produced [97], though the racemic form has also been obtained [98]. Further work of a similar nature has also been carried out, but the results do not differ very markedly from the typical cases quoted above [99].

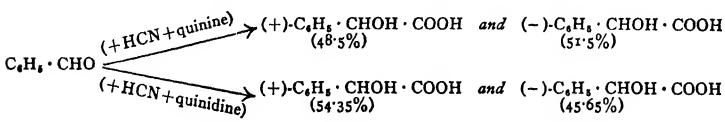
Most striking of all, however, is Neuberg's work on the very widely occurring enzymes known generally as the "*ketonaldehydemutases*", whose chief function is to transform the labile hydrates of certain keto-aldehydes into stable hydroxy-acids, with the production of an asymmetric carbon atom [100]. The reaction is really a simultaneous oxidation and reduction, and has been termed an "internal Cannizzaro reaction".



The striking feature of this work lies in the extremely one-sided nature of the addition of the elements of water to the substrate. Practically theoretical yields of the resulting hydroxy-acid, of 100 per cent optical purity, have several times been obtained, and indicate, on the basis of Bredig's previously discussed work, an extremely wide

divergence in the rates of formation from the substrate of the two antipodal forms, one being formed in negligible amount. Thus, methyl-glyoxal has been converted almost quantitatively into lactic acid, whose optical activity varied from zero up to 100 per cent optical purity, according to the source of the enzyme, which also affected the *sign* of rotation of the product [101]. Equally striking analogous results have been obtained by the dismutation of phenyl-glyoxal to optically active mandelic acid [102]. The work has also been extended to derivatives of methyl-glyoxal, a quantitative dismutation of methyl-glyoxal-acetic acid to (+)-*a*-hydroxy-glutaric acid, of 90 per cent optical purity, having been observed [103].

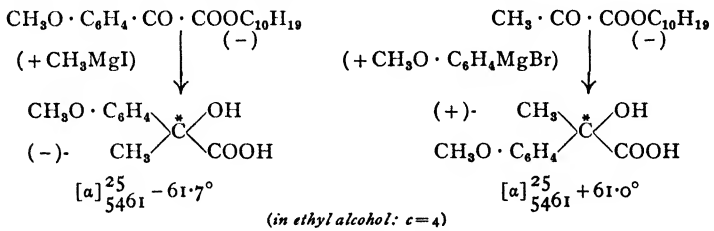
It will at once be seen from the foregoing sections that there is, superficially, a great difference between the two types of partial asymmetric synthesis so far realised in the laboratory. In all cases where the directing agent was of known constitution, and where the synthesis was effected *in vitro* under "artificial" conditions, as opposed to those obtaining *in vivo*, the excess of one optical antipode was relatively small. In the asymmetric synthesis of mandelic acid realised by Bredig and Fiske [72], for example, the excess of one antipode over the other amounted to only a few per cent:



Similarly, in the asymmetric syntheses carried out by McKenzie, the excess of one antipode was still relatively small, though in many cases it exceeded the above quantities very considerably.

In cases, however, where the directing agent was a complex natural product of unknown constitution, the relative excess was in general far more striking: and, as already stated, one antipode was often produced to the virtual exclusion of the other, thereby demonstrating the greater efficiency of the asymmetric enzymic processes evolved by the living organism.

It should be noted, however, that McKenzie and Ritchie [48] have recently succeeded in isolating the optically pure antipodal forms of a substituted glycollic acid, by repeated crystallisation of the products of two partial asymmetric syntheses of the first type. In all previous asymmetric syntheses by the Grignard reaction, crystallisation of the resulting optically active acid mixture led to the separation of the racemate: the excess of the (−)- or (+)-antipode remained in the mother liquors, and was never isolated in a state of optical purity. The above-mentioned result, however, was observed during the asymmetric synthesis of methyl-anisyl-glycollic acid by the following pair of reactions:



In the case of this particular acid, it was found that

on crystallisation from benzene, the *r*-acid remained in the mother-liquors, and the excess of the (−)- or (+)-antipode separated out. On repeated crystallisation of the crude products, small samples of the (−)- and (+)-acids were isolated, whose rotatory power and melting point did not alter on further crystallisation. It seems, therefore, highly probable that optical purity has been attained in the above products of a laboratory asymmetric synthesis—a very interesting result.

Let us now sum up the position in the light of all the foregoing results. In the first place, a great weight of experimental evidence indicates that a *completely* selective asymmetric synthesis (or decomposition) probably does not occur in natural processes. Nevertheless, the enzymic syntheses of Neuberg show that there is no difficulty in accepting the well-known fact that optically pure substances are of very widespread occurrence in nature. Natural synthesis can never lead to a state of completed chemical equilibrium: the organism cannot stop its physiological functions to wait till equilibrium has been established in these relatively slow organic reactions. The life process involves the mutual regulation of many interdependent reaction velocities: a static and complete "reaction equilibrium" is never reached, but only what Jaeger terms a kind of apparent "dynamical constancy" [104]. While one antipode is taking part successfully in the cell metabolism, for example, the other is being formed simultaneously in incomparably smaller quantities —or, what amounts to the same thing, at a very much smaller speed—and is almost certainly being eliminated as rapidly as it is formed, by some side-

reaction. Ages of evolution have adapted the physiological behaviour of the organism to the use of one antipode alone. The formation of one antipode to the apparent exclusion of the other is due merely to a difference in reaction velocities.

It is now perfectly obvious, in the light of all the above results, that a pre-existing molecular dissymmetry has a definite directing influence upon subsequent syntheses whereby a new asymmetric centre is created in some other part of the molecule. Theoretically, we can now see that once a single optically active compound has been synthesised by some agency or other, its asymmetry can be propagated to other compounds by syntheses of the type described above. From these, other and more diverse types of optically active compounds could arise: indeed, in the course of ages of evolution, it is quite possible to see how, from one simple optically active substance, reactions of gradually increasing complexity may have given rise to the multitude of natural optically active products occurring at the present day.

We have still, however, to get at the root of the matter. In all the artificial laboratory syntheses already described, the directing influence has been some natural optically active product, or an active substance produced in the laboratory by the aid of such a natural product. The directing agent is itself, therefore, the final stage in a series of natural asymmetric syntheses, extending possibly over a period of many millions of years. What was the dissymmetrical agency which started such a synthetic chain? Whence came the first optically active sub-

stance, which, on the above hypothesis, could account for all subsequent elaborations? Unless we accept the extremely unsatisfactory and unlikely theory of a purely chance synthesis—a chemical coincidence—we are forced to regard the initial synthesis as having occurred under the influence of some naturally occurring dissymmetrical physical agency. It was therefore of fundamental interest to carry out what is, perhaps, best termed an "*absolute asymmetric synthesis*": and many workers have attacked this problem.

IV

ABSOLUTE ASYMMETRIC SYNTHESIS

It has been recognised for a long time that sunlight, reflected by the surface of the sea, is always partially elliptically polarised [105], as a result of the terrestrial magnetic field [106]. Further, van 't Hoff made the suggestion that optically active substances might be formed in nature—

> bei unsymmetrischen Versuchsbedingungen, bei Umwandlungen, z.B. die durch die Wirkung des rechts- oder linkscirkularpolarisierten Lichtes stattfinden.[107] . . .

It remained for Byk [108] to connect these two ideas by pointing out that since *dextro*-circularly polarised light predominates at the earth's surface in reflected sunlight, an unsymmetrical form of solar photochemical energy has been available, during countless ages of evolution, for the multitude of vital syntheses which are carried out in living cells under the influence of sunlight. This suggested, obviously, certain lines of attack upon the problem of absolute asymmetric synthesis: while a different method was suggested by Pasteur, who considered that vital asymmetric syntheses might possibly be imitated by carrying out the appropriate reactions in a magnetic field, as well as under the conditions suggested above. Indeed, it is recorded [109] that he provided himself with a powerful electromagnet for this purpose, though no results were published.

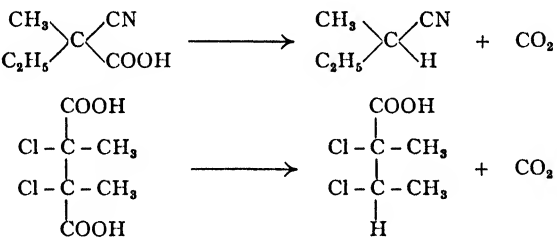
Many experiments on these lines are described

in the literature: but for many years all attempts met with complete failure, largely because they were based upon an incomplete apprehension of what constituted a truly unsymmetrical set of reaction conditions. Boyd [110], for example, carried out the reduction of benzoylformic acid in a strong magnetic field, and also studied the bromination of stilbene under the same conditions, with completely negative results. This, however, was only to be expected, since a homogeneous magnetic field, as pointed out by Meyer [111], is not itself asymmetric, but merely polar, having a plane of symmetry perpendicular to its lines of force. Curie [112], however, in a discussion of asymmetry in physical phenomena, had already pointed out that superimposed magnetic and electrostatic fields constitute an unsymmetrical physical agency: and the same end can be attained by passing a beam of plane-polarised light through a magnetic field, parallel to its lines of force.* Meyer himself reduced (+)-amyl benzoylformate with sodium amalgam, under the latter set of conditions: but only (+)-amyl *r*-mandelate was isolated. Similarly, Guye and Drouginine [114] found that the bromination of methyl fumarate (or cinnamate) under the former set of conditions gave a negative result. And here, again, such results were only to be expected: for although the physical directing influences employed were now truly asymmetric, they were not essential conditions for the initiation

* In the light of Curie's remarks, of course, the failure of Pasteur's earlier experiments at the Ecole Normale Supérieure was inevitable. The crystallisation of racemic substances in a magnetic field (later repeated by Boyd [113]), and the attempt to render a compound optically active by placing it in a rapidly rotating tube, were both based on false conceptions of asymmetry.

of the reaction. As summarised by Jaeger [115], "the necessary conditions will be such that the externally applied forces are a *conditio sine qua non* for the initiation of the reaction which would be impossible without them. Furthermore, these external forces must be of a symmetry sufficiently low to form a system of directional forces different from its mirror image."

A better-conceived experiment was carried out by Henle and Haakh [116], who eliminated carbon dioxide from certain racemic carboxylic acids in the presence of uranium salts as catalysts, under the influence of light, thus:



The light employed was either circularly polarised by $\frac{1}{4}$-λ mica plates, or plane polarised and then passed through a magnetic field: but only racemic products were obtained. Byk has published an interesting comment on this result [117].

About the same time, Padoa [118] brominated a solution of angelic acid in carbon disulphide, under the influence of circularly polarised light: and a more recent experiment by Pirak [119] involved the addition of hydrocyanic acid to acetaldehyde under the same conditions. Both attempts, however, met with complete failure.

The experiments of Rosenthal [120] may be neglected

here: his claim to have effected the asymmetric hydrolysis of certain complex carbohydrates in an oscillatory electromagnetic field was not confirmed by later investigators.

Thus, all attempts to realise an absolute asymmetric *synthesis* under controlled laboratory conditions have so far been unsuccessful. Nevertheless, a fundamental advance has recently been made, whereby the asymmetric photochemical *decomposition* of several externally compensated compounds has at last been conclusively demonstrated. In the strict sense of Marckwald's definition, of course, this is not an asymmetric synthesis, since no new asymmetric carbon atom has been produced. It constitutes, however, a clear-cut case of the production of an optically active from a racemic substance, comparable to selective enzymic decompositions, but taking place under the influence of a naturally occurring physical directing agency—circularly polarised light. This result is of such fundamental interest that it will be considered here in some detail.

In the complex absorption spectrum of an optically active organic compound, at least one of the bands is of optically active origin—that is to say, it is due to an electronic system which, in addition, contributes a definite partial rotation to the optical rotatory power of the molecule. The curve of rotatory dispersion displays complete anomaly in passing through such a band, which, however, usually represents only a small fraction of the total optical absorption of the molecule.

As far back as 1896, Cotton [121] showed that in the immediate neighbourhood of such a band circular

dichroism (the "*Cotton effect*") will be manifested. A simple example will best illustrate what this means. Suppose, for the sake of simplicity, that we pass a beam of plane-polarised white light through

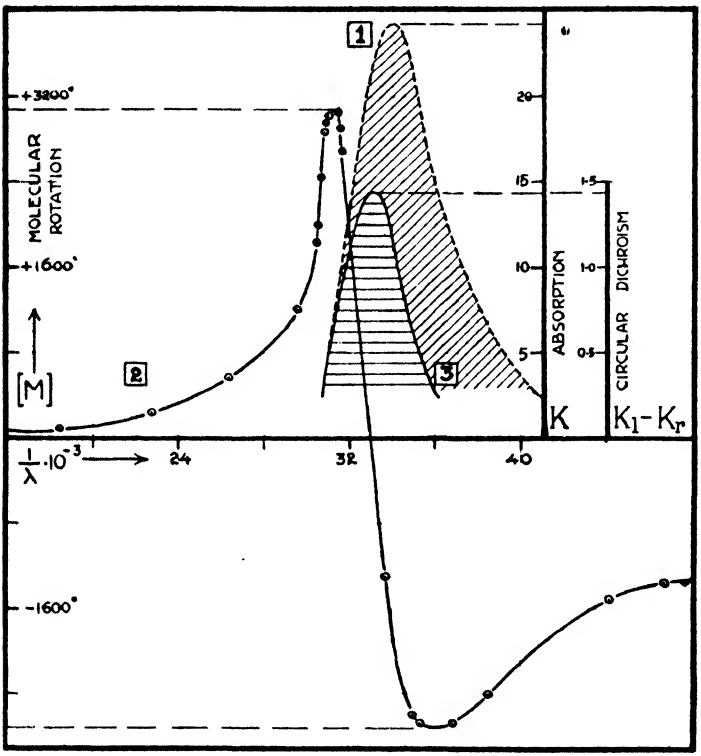


FIGURE I.

Camphor in Hexane

(1) Absorption. (2) Rotatory Dispersion. (3) Circular Dichroism.

an optically active medium, whose absorption spectrum contains only *one* band of optically active origin, with its absorption maximum at λ_m. It will then be found that the emergent beam is still plane polarised for all wave-lengths, except those in the

neighbourhood of λ_m, where it is now elliptically polarised, with maximum ellipticity at λ_m. Conversely, if we irradiate such a medium with *dextro*- and with *lævo*-circularly polarised light, we find that the two incident beams are unequally absorbed in the neighbourhood of λ_m, while for all other wavelengths the two absorption coefficients (ϵ_r and ϵ_l respectively) are equal. Figure I, which is due to Kuhn [122], shows a typical case of circular dichroism and anomalous rotatory dispersion in the neighbourhood of an optically active absorption band situated in the ultra-violet.

Now, on the basis of Fresnel's classical explanation of optical rotation, the above results indicate that the two oppositely rotating circularly polarised components of the incident plane polarised beam, of wave-length λ_m, have been unequally absorbed by the active medium. If, therefore, this circular dichroism occurs at, or near, the optimum wavelength for photochemical decomposition of the medium, it will be seen that an asymmetric bias might be imparted to such a reaction. The actual magnitude of such a bias would be proportional to the relative difference between the extinction coefficients of the pure active substance for *dextro*- and *lævo*-circularly polarised light. This difference is known as the *anisotropy factor*:

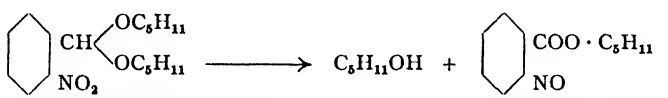
$$g = \frac{\epsilon_l - \epsilon_r}{\epsilon}$$

(*where* $\epsilon = \frac{1}{2}(\epsilon_l + \epsilon_r)$ = *absorption coefficient for ordinary light*)

Cotton showed that alkaline solutions of copper (or chromium) (+)- and (−)-tartrates exhibit such a circular dichroism for red light [123]. Since these solutions undergo reduction in sunlight, Cotton

tried to effect this decomposition asymmetrically, by irradiating the racemates with *dextro-* and with *lævo*-circularly polarised sunlight: but no resulting excess of an active tartrate could be detected, even after prolonged irradiation. According to more recent conclusions, however, such a result was only to be expected. In the first place, Byk [108] demonstrated that the observed photochemical reduction is effected only by the ultra-violet components of sunlight: while Mitchell [17] has more recently shown that Cotton's tartrate solutions exhibit circular dichroism *only* at the red end of the spectrum.

Byk [108], Freundler [124], and Bredig [125], working on the lines indicated by Cotton in 1896, subsequently carried out a variety of photochemical decompositions: but all results were negative, most probably for reasons similar to that outlined above. Byk exposed optically active photographic preparations (silver tartrate paper, and silver bromide plates sensitised with chlorophyll) to *dextro-* and to *lævo*-circularly polarised light of the same intensity: but the resulting images were identical. Freundler brought about the following curious photochemical decomposition by the action of circularly polarised light:



(*r-o-nitro-benzaldehyde-diamyl-acetal*) (*amyl-o-nitrosobenzoate*)

but only racemic products were obtained. Bredig's experiments involved the decomposition of diazo-camphor, lactic acid, and various racemic cobalt-ammine salts by circularly polarised ultra-violet light: but once again the results were negative.

It may also be mentioned that McKenzie, in 1895, had carried out some unpublished experiments on the action of circularly polarised light on solutions of inactive silver lactate and mandelate: but the results were negatived.

One further unsuccessful attempt is worthy of mention. Jaeger [126] examined the photochemical decomposition of (+)- and (−)-potassium trioxalato-cobaltiate:

$$2K_3(Co^{III}(C_2O_4)_3) \longrightarrow 3K_2C_2O_4 + 2Co^{II}C_2O_4 + 2CO_2$$

under the influence of *dextro*- and of *lævo*-circularly polarised light, but failed to detect any differences in velocity of decomposition.

In 1929, however, Kuhn and Braun [15] at last obtained a very faintly active product by the photochemical decomposition of optically inactive ethyl *a*-bromopropionate, $CH_3 \cdot \dot{C}HBr \cdot COOC_2H_5$, with circularly polarised light (λ2800). The greatest observed rotation was, however, only $\pm 0{\cdot}05°$, and the nature of the complex decomposition was not elucidated: but, more recently, Kuhn and Knopf [16] have carried out the first really conclusive experiment, which is worthy of closer consideration.

Starting with the fact that the extent of the activation, produced by such a photochemical decomposition, is proportional to the *anisotropy factor*, g, Kuhn has shown that the actual optical rotation of the activated substance, in a polarimeter tube of known length, can be expressed by

$$\gamma = \Gamma \frac{g}{2} (1-a) ln \frac{1}{1-a} \quad . \quad . \quad . \quad . \quad . \quad (i)$$

where Γ is the rotation shown by the optically pure substance in a tube of the same length, and *a* is the degree to which the decomposition has proceeded.

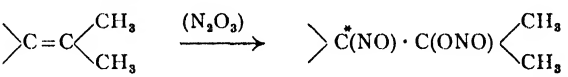
Now, it was found that *a*-azido-propionic-dimethylamide, $CH_3 \cdot \dot{C}HN_3 \cdot CO \cdot N(CH_3)_2$, exhibits a weak ultra-violet absorption band at λ2900, which can be attributed with certainty to the azido group, N_3. In its neighbourhood, the antipodal forms of the amide displayed completely anomalous rotatory dispersion, and marked circular dichroism. The absorption coefficients of the pure active form for *dextro-* and *lævo*-circularly polarised light, within the region of this absorption band, differ by 2·4 per cent—that is, $g = 0{\cdot}024$.

On irradiation with *dextro*-circularly polarised light, of wave-length 2800-3100 Å, the inactive amide decomposed, with liberation of one molecule of nitrogen per molecule of amide, and formation of *as*-dimethyl urea, and, probably, ethylene-urea. When examined in a 1 dcm. tube, the recovered (unattacked) amide showed $a_{5791} + 0{\cdot}78°$: while, when *lævo*-circularly polarised light was employed for the decomposition, the product now showed $a_{5791} - 1{\cdot}04°$.

From formula (i), with $\Gamma = 340°$, $g = 0{\cdot}024$, and $a = 0{\cdot}4$ (= 40 per cent decomposition), we get $a_{calc} = 1{\cdot}25°$—a very satisfactory agreement between experiment and theory, considering that the light employed was not completely circularly polarised. The signs of the observed rotations, too, agree with those predicted. Further, it was shown that Einstein's Equivalence Law is approximately fulfilled in this decomposition—that is, only one molecule of amide was decomposed for each absorbed light quantum, no "chain reaction" taking place—which is a necessary condition for the validity of the above quantitative estimations. Though the

observed rotations correspond to only 0·5 per cent excess of the (+)-amide, Kuhn showed that, by practically complete decomposition, an almost optically pure product could theoretically be obtained.

These remarkable results were confirmed by the slightly later results of Mitchell [17], who effected the asymmetric photochemical decomposition of humulene nitrosite, $C_{15}H_{24} \cdot N_2O_3$, by circularly polarised red light. Humulene is an inactive sesquiterpene, combining with nitrous anhydride to form a coloured racemic nitrosite:



This decomposed on irradiation with circularly polarised light, a maximum rotation of α (Hg yellow) $\pm 0{\cdot}30^\circ$ being observed, which fell again to zero in 64 hours. Since, however, we are dealing here with compounds of doubtful constitution and unknown optical properties, this case is perhaps not quite so convincing as that quoted above.

We have, therefore, at last obtained definite proof that it is possible to produce optically active compounds by means of naturally occurring unsymmetrical physical agencies, without the intervention of Life, starting from optically inactive materials of a certain type. In other words, a possible and probable genesis of optical activity in natural products has been duplicated under laboratory conditions—surely a landmark in stereochemistry.

If we hark back for a moment to Fischer's conception of vital synthesis in green plants, we see that we need no longer consider the optically active

chlorophyll granules* as the directing influence in the asymmetric synthesis of plant products—or, at least, as the only such influence. The natural condensation of formaldehyde to sugars is supposed to be largely photochemical in nature: and the presence in direct sunlight of even a small proportion of reflected, diffused sunlight, circularly polarised as already described, might well be sufficient to give the synthesis its initial unsymmetrical bias.

It will be remembered that Baly, Heilbron, and Barker [127] have examined the photosynthesis of formaldehyde from carbon dioxide and water, and the polymerisation of the product with formation of carbohydrates. Both reactions, they found, could be photocatalysed by certain coloured basic substances, such as malachite green or colloidal ferric hydroxide: and, pursuing this idea, they suggest that "the use of chlorophyll at once introduces the possibility of the synthesis of optically active sugars".

It may be noted in passing that Zocher and Coper [128] irradiated a thin layer of silver halide with circularly polarised light, and obtained a layer of silver which rotated plane polarised light, with production of elliptical polarisation in the trans-

* Until recently, there has been a certain amount of doubt about the supposed optical activity of chlorophyll [279]. Stoll and Wiedemann [280] have, however, shown that chlorophyll "*a*" and chlorophyll "*b*" are both lævorotatory. This, of course, might have been due to the optically active phytyl radical, which forms an integral part of the chlorophyll molecule, and which is unlikely to be essential to photosynthetic action. But phäophorbide "*a*" and phäophorbide "*b*" were also shown to be lævorotatory: and these substances are actually the phytol- and magnesium-free derivatives of the corresponding chlorophylls, which must therefore contain one or more optically active centres apart from the phytyl radicals.

mitted beam. This, of course, is not an asymmetric synthesis: but it exemplifies the artificial formation of an asymmetric arrangement of molecules which are themselves symmetrical. It recalls an early experiment by Kipping and Pope [129], who crystallised sodium chlorate from aqueous solutions of (+)-glucose, or of (−)-fructose, and obtained an excess of right-handed over left-handed hemihedral crystals in the resulting crop.

This leads us to the consideration of one final group of experiments—namely, the work of Ostromisslensky on the crystallisation of racemates [130]. The outstanding result in this work is the fact that a supersaturated solution of *r*-asparagine, on inoculation with a crystal of glycine (which, of course, contains no asymmetric carbon atom), deposits preferentially only *one* antipode. This was attributed to the existence of hemihedrism in crystals of glycine, though this phenomenon has not yet been definitely demonstrated. If this result could be definitely substantiated, we would have here another possible genesis of optically active products in nature: but much of Ostromisslensky's work is indefinite, and requires confirmation. The position has been summed up by Jaeger [131] thus:

> One may ascribe . . . probability to the supposition that the exclusive separation of one of the antipodes in its field of stable existence, was due to a germ of an inactive, but hemihedrally crystallising substance, such as glycocoll, coming into contact with supersaturated solutions. . . . If this phenomenon took place within a vegetable cell whose contained solutions were supersaturated with some organic compound resolvable by spontaneous crystallisation under the prevailing conditions, it would be at least conceivable

that in this way an optically-active antipode might come to be incorporated in the cell, thus determining its one-sided synthesis for all future generations. Ostromisslensky's experiments need further corroboration, however. . . . Until this has been done, we are inclined to look for physical causes outside of the living organism, and in such a search the greater chance of discovering the correct cause is undoubtedly in the field of photochemical phenomena.

This opinion was, of course, strikingly confirmed by the photochemical decompositions of Kuhn, and of Mitchell, previously described: but an alternative suggestion has quite recently been put forward. In his address to the Chemistry Section at the 1932 meeting of the British Association, W. H. Mills [132] discussed the origin of optical activity in living matter, and expressed a certain scepticism of any explanation based on the action of circularly polarised light. His objections were founded, not without some justice, on "the minuteness of the proportion of the total illumination received by an organism under natural conditions that can be circularly polarised, and the difficulty that has been experienced in demonstrating the optically activating effect of this form of light, even under the favourable conditions of the laboratory". He put forward the novel suggestion that *the optical activity of living matter is an inevitable consequence of its property of growth.* His argument was built up in three stages:

(i) If we consider the known stereo-specificity of the reactions of living matter, the conclusion is justified that such reactions are far more efficient than they would be if only racemic reagents were involved. By cautious applica-

tion of the law of mass action to enzymic processes, it can, for example, be shown that "the inactivation of living matter by the instantaneous replacement of half of each of its optically active components by their enantiomorphs would suddenly diminish the rates of all the stereo-specific reactions proceeding in it to rates approximating more or less, in the case of reactions of bimolecular type, to one-half of their former magnitudes".

(ii) It follows, therefore, that if a growing tissue were not *completely* optically inactive, the slightest departure from exact equality of the (+)- and (−)-components "would increase with growth continually, according to a compound interest law until, eventually, the system originally in slight defect was completely swamped by its enantiomorph". An optically inactive growing tissue would therefore be, as regards its optical inactivity, in a state of unstable equilibrium.

(iii) The above arguments have no particular novelty: they have been put forward more than once in the past, in varying forms. Mills, however, pushed the matter further. He suggested that when large numbers of molecules of a racemic compound are synthesised under undirected conditions, the probability that *exactly* equal numbers of the two antipodal molecules will be produced is very small—that, indeed, such an exact distribution between the (+)- and (−)-forms will practically never occur. Calculations were put forward, whereby it was concluded that

when (to take a concrete example) ten million dissymmetric molecules are produced under symmetrical reaction conditions, "there is an even chance that the product will contain an excess of more than 0·021 per cent of one enantiomorph or the other. It is practically impossible for the product to be absolutely optically inactive. . . . If we could assume, therefore, that the first portion of living matter which arose on this planet was of microscopic dimensions, we might account on the basis of the laws of probability for the existence of a minute initial bias towards one optical system or the other; and this would then, if the principles which I have endeavoured to explain are justified, eventually lead to the complete optical activity of the molecularly dissymmetric components of all living matter. The development of the organic kingdom from a single germ would provide a simple explanation of the configurational relationship which appears to exist between the optically active components of the most diverse forms of life, as is illustrated by the occurrence in Nature of glucose in its dextro-rotatory form only. The mystery of living matter seems to lie in its power of growth. Given this, the optical activity of its components appears to follow as a necessary consequence of the law of mass action and the stereo-specificity of interactions between dissymmetric compounds."

The whole conception is extremely interesting,

and well worthy of close consideration, although Mills continually emphasises the tentative nature of his suggestions, which are advanced with considerable caution and reserve. To the present author, however, it seems a little unconvincing to attribute the asymmetry of natural products to such a purely fortuitous initial bias. If, for example, several microscopic portions of living matter arose independently, at different portions of this planet, surely the (say) dextro-system initiated by chance in one of these primitive complexes would be balanced by a lævo-system in another. Though the *existence* of an initial bias could probably be explained on Mills'' hypothesis, there is no reason why its asymmetric *sense* should not vary haphazard in passing from one to another of several minute living and growing complexes, perhaps separated from one another by thousands of miles. It is difficult, therefore, to explain the almost entirely one-sided picture which is presented to-day by natural products in all parts of the world.

It seems to the writer more rational, and more convincing, to attribute the one-sided system of nature to the influence of some such physical agency as circularly polarised light: for this, at least, has presented a constant and unvarying asymmetric directing influence throughout untold ages of evolution. This latter theory has, too, a certain experimental backing: whereas it would appear almost out of the question to verify the alternative hypothesis by direct experiment.

PART II

ASYMMETRIC INDUCTION

I

A CRITICAL SURVEY OF EVIDENCE BEARING UPON THE CONCEPTION OF ASYMMETRIC INDUCTION

In any given asymmetric synthesis, it is obvious that the spatial configuration of the final product must be determined in some definite way by that of the compound which acts as the optically active directing agent. A survey of the various asymmetric syntheses described in the foregoing pages will show, however, that there is no very obvious superficial connection between these two configurations. There is not, for example, any real regularity in the relationship between the algebraic signs of the two corresponding optical rotations. Read and McMath[133] point out that "the optically active product exhibits in the great majority of instances the same sense of rotation as the directive asymmetric system": but there are, of course, many exceptions, and this statement is not intended as a general rule. No such regularity could, indeed, be expected: for even in a series of configuratively related compounds, the optical rotations vary in sign in a manner which has never yet been covered by a really comprehensive generalisation. It becomes of interest, therefore, to attempt to discover some possible mechanism underlying asymmetric synthesis in general, whereby the optical activity of the product can be correlated with that of the directing system: and we must, in particular, review the hypothesis of "*asymmetric induction*".

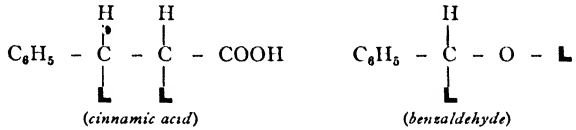
Asymmetric induction has been defined by

Kortüm [134] as the action of a force, arising in all asymmetric systems, which influences certain adjacent systems, originally of symmetrical configuration, in such a way that they become asymmetric. He points out that the definition covers two types of asymmetric induction—"intramolecular", and "intermolecular"—according to whether the two systems involved are in the same or different molecules.

The idea can be traced as far back as 1892, when it was tentatively suggested by Le Bel [135] that an unsaturated ethylenic double bond might act as a centre of optical activity: but it was not till 1911 that Emil Erlenmeyer, Junior, definitely enunciated the hypothesis of "asymmetric induction". From that year until his death in 1921, a striking series of papers appeared under his name, bearing upon this subject [136]. Erlenmeyer supposed that certain unsaturated compounds, containing no classical asymmetric carbon atom, could yet exhibit molecular asymmetry, and hence exist in optically active forms. The general failure to detect such optical activity was attributed to the small degree of mechanical stability, and consequent ready racemisation, of compounds of this type: but experimental evidence was later submitted for the isolation of cinnamic acid, and of benzaldehyde, in optically active forms.

On classical stereochemical theory, a *cis*- and a *trans*-form of cinnamic acid should exist: but in addition to the latter, three distinct modifications of the *cis*-acid are actually known. This is regarded as a case of trimorphism [137]; and Erlenmeyer developed an explanation on the grounds of "relative

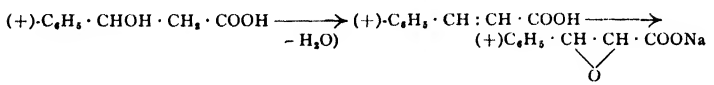
isomerism" [138]. He represented cinnamic acid, and similar unsaturated compounds, by his well-known "Lückenformeln", where ▙ represents an unattached valency bond:



On this representation, cinnamic acid should exist as a series of twelve "relative isomers", certain of which should display molecular asymmetry, and therefore potential optical activity. It is interesting to note that Allen [139] has developed a theory of optical rotation on the basis of which eight isomers of cinnamic acid could possibly exist.

Erlenmeyer's claims have, however, met with very adverse criticism: and it seems desirable to examine them here in some detail.

The dehydration of optically active β-phenyl-β-hydroxy-propionic acid was first carried out [140]. The resulting product was mostly optically inactive: but in one case Erlenmeyer obtained from the initial dextrorotatory acid a sample of cinnamic acid which displayed a slight dextrorotation, which was magnified on converting the product to sodium phenoxyacrylate, thus:



But Erlenmeyer's experimental conditions were such that the optical activity might quite well have been due to a trace of the unattacked hydroxy acid: and after a recent careful repetition of the above

dehydration, McKenzie and Mitchell were unable to confirm Erlenmeyer's result [141].

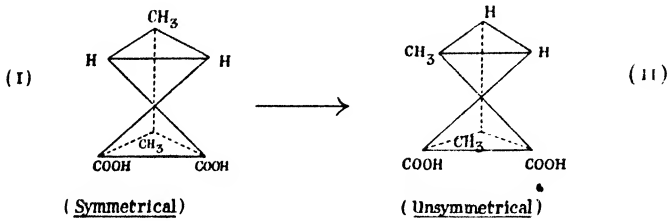
Next, Erlenmeyer claimed to have produced an optically active cinnamic acid by fusing the ordinary (inactive) form with tartaric acid, or with (+)-phenyl-lactic acid [142]. When, for example, (+)-tartaric acid was employed, the cinnamic acid extracted from the fusion mixture had, apparently, a distinct lævorotation: while a dextrorotatory cinnamic acid was obtained by using (−)-tartaric acid. It was claimed that the product was free from tartaric acid: and the fact that the optical rotation of the product was of opposite sign from that of the tartaric acid employed seems to indicate that, in this case at least, the activity cannot be due to unremoved traces of the initial active acid. In a recent paper, however, Ebert and Kortüm [143] have repeated and critically examined these experiments: and they appear to have established that the activity of the product is associated with a substance which does not have the analytical composition of cinnamic acid—probably a cinnamate of tartaric acid.

Erlenmeyer's experiments were extended to include benzaldehyde, an optically active form of which was apparently obtained by heating the aldehyde with tartaric acid in alcoholic solution [144]. (+)-Tartaric acid gave rise to a small proportion of a lævorotatory benzaldehyde: addition of hydrocyanic acic then yielded (−)-mandelonitrile, which on hydrolysis yielded (+)-mandelic acid. This result was adversely criticised by Wedekind [145], who claimed to have shown that the slight activity of Erlenmeyer's benzaldehyde was due in reality to an oily condensation product of tartaric acid and

benzaldehyde. The latter author replied by quoting analyses of the various active samples obtained, which, it was claimed, eliminated the possibility that sufficient impurities were present to impart any optical activity [146].

Reviewing the above experiments of Erlenmeyer, it is perhaps not unfair to say that his evidence for the existence of an optically active form of cinnamic acid rests on an insecure experimental foundation, as does his original claim to have isolated a *stable* optically active benzaldehyde—a claim, be it noted, which he was unable to verify later on. Nevertheless, the possibility is not excluded that a labile form of the latter, with a very transient asymmetry, had been obtained, since it must be remembered that this product definitely gave rise to optically active mandelonitrile and mandelic acid.

Erlenmeyer made various ingenious extensions of his theory of asymmetric induction, applying the conception to the mechanism of the Walden inversion [147], as well as to asymmetric synthesis and the formation of optically active compounds in nature [148]. He repeated and confirmed Marckwald's synthesis of optically active valeric acid [34] (see p. 17). In addition, he obtained (−)-valeric acid by heating one equivalent of (+)-tartaric acid with methyl-ethyl-malonic acid: and, in a similar way, (+)-valeric acid was obtained by using (−)-tartaric acid. Erlenmeyer explained these syntheses on the basis of asymmetric induction: he assumed that the symmetrical molecule of methyl-ethyl-malonic acid, under the influence of the added directing agent, assumed in solution an asymmetric configuration, thus:



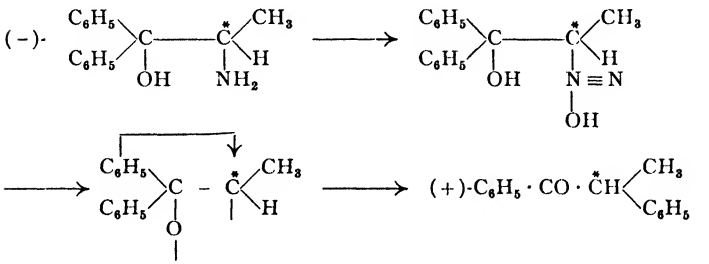
The two -COOH groups in (II) are no longer equivalent, possessing, for example, different velocities of esterification. As shown on p. 20, however, this asymmetric synthesis can be explained without utilising the hypothesis of asymmetric induction.

Results rather analogous to the above were quoted in Erlenmeyer's last published paper on this subject [149]. Here, it was claimed that (-)-$\alpha\beta$-dibromo-β-phenylpropionic acid was obtained by the bromination of cinnamic acid in the presence of glucose, fructose, or sucrose: while the (+)-acid was obtained in the presence of arabinose. Erlenmeyer's untimely death in 1921 unfortunately cut short this line of research just when it seemed that positive results were at last being obtained.

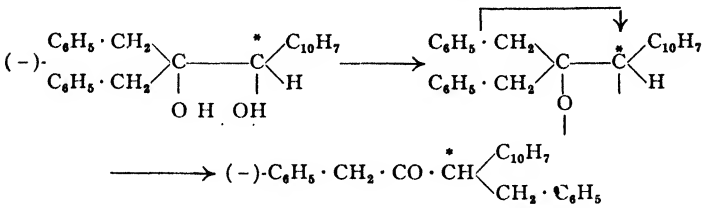
Recently, his son has published the result of certain experiments bearing upon the same problem, along with an interesting theoretical discussion upon "dynamic stereochemistry" [150]. Bromination of (+)-cinchotine cinnamate, in chloroform solution, was found to yield optically active $\alpha\beta$-dibromo-β-phenylpropionic acid, containing 57·8-58·3 per cent of the (+)-antipode. This proportion fell to 51·3-51·9 per cent on carrying out the bromination in the solid phase: and similar results were observed with (+)-glucosamine cinnamate. Hans Erlenmeyer therefore concluded that in such an asymmetric synthesis

the transference of asymmetry proceeds more readily with "amorphous" molecules, in solution, than with molecules regularly disposed in a crystal lattice. These molecules, therefore, are not identical: they possess different stereochemical configurations, which may perhaps be explained on the earlier basis of "relative isomerism".

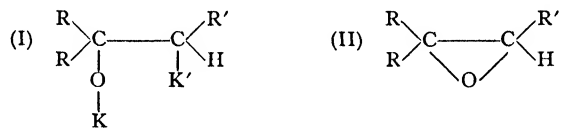
Erlenmeyer's *Lückenformeln*, which at the time had no very precise physical significance, receive a certain amount of support from modern conceptions. Pauly [151] made a tentative suggestion that the free valency bands, represented by ⌊, might be linked to electrons: and a somewhat similar scheme has more recently been devised by McKenzie to explain the retention of optical activity in ketones produced by semi-pinacolinic changes. Here, an electric charge is supposed to play the part of a radical in retaining the asymmetry of the carbonium ion which apparently occurs as a transient intermediate stage in the reaction. Thus, the semi-pinacolinic *deamination* of (−)-2-methyl-2-amino-1 : 1-diphenyl-ethanol-(1) [152] may be represented as follows:



and the semi-pinacolinic *dehydration* of (−)-2-*a*-naphthyl-2-hydroxy-1 : 1-dibenzyl-ethanol-(1) [153] as follows:



An ion of type (I) is postulated as an intermediate stage. In order to account for the retention of asymmetry, and the non-formation of the stable ethylenic oxide (II), McKenzie, Roger, and Wills [152] felt compelled to make the assumption—"a very problematical one"—that the two postulated electric charges, K and K′, were of the same sign.

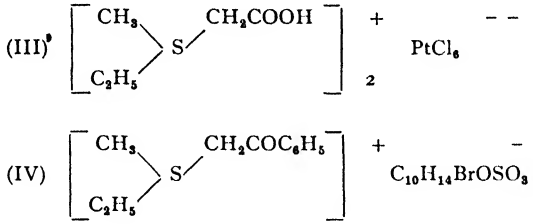


The above mechanism has been criticised, on the grounds of recent electronic theory, by Kenyon, Lipscomb, and Phillips [154]: but their alternative scheme is not entirely satisfactory. It does not demonstrate clearly the necessity for the migration of a radical, nor does it convince one that the final stage can occur without the formation of a transient carbonium ion [155].

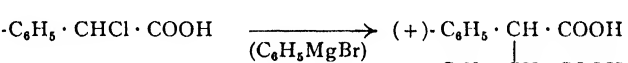
An analogous suggestion has been put forward by Walden [156], to explain the optical activity of the methyl-ethyl-thetine and methyl-ethyl-phenacyl-sulphine ions in the complexes described by Pope and Peachey [52] (III) and Smiles [157] (IV). To account for the retention of asymmetry in these ions, the following explanation was advanced by Walden:

Vom asymmetrischen Schwefel-, Selen-, und Zinnatom

sind aber die optisch-aktiven Atome in chemischungesättigter Form, also *dreiwertig* mit einer freien Valenz, als *Kationen* unter Verlust eines Valenzelektrons, erhalten worden. . . .

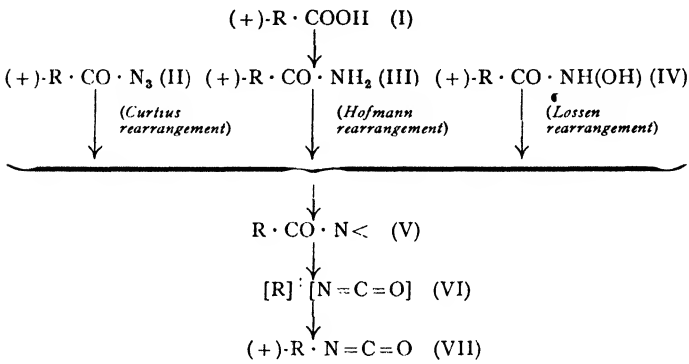


It is possible that a similar cause is responsible for the retention of optical activity in the following change, observed by McKenzie, Drew, and Martin [158]:

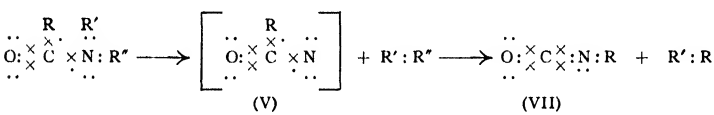


Further evidence, which may be held to confirm the existence of such ions, has been obtained by the examination of various optically active derivatives of (+)-benzyl-methyl-acetic acid (I). Jones and Wallis [159], for example, have effected the Curtius (or Beckmann) rearrangement of (+)-benzyl-methyl acetazide (II) to (+)-benzyl-methyl-isocyanate (VII): and Wallis and Nagel [160] found that (+)-benzyl-methyl-acetamide (III) undergoes the Hofmann rearrangement with formation of (+)-benzyl-methyl-methylamine, which, of course, involves the intermediate formation of the (+)-isocyanate (VII). More recently, also, Wallis and Dripps [281] have demonstrated the formation of the (+)-isocyanate (VII) when (+)-benzyl-methyl-hydroxamic acid (IV) undergoes the Lossen rearrangement. These

transformations may be represented by the following scheme, where $R = C_6H_5 \cdot CH_2 - \underset{|}{CH} - CH_3$:



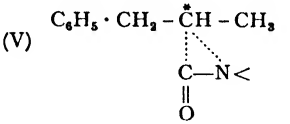
As pointed out by Stieglitz, there is a fundamental resemblance between these three allied rearrangements. All involve, apparently, the intermediate formation of the complex (V), containing an atom of univalent nitrogen:



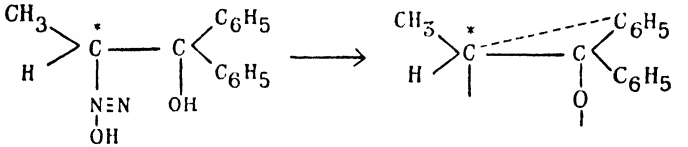
In each case, the ultimate production of an optically active compound must be explained by the retention of asymmetry in the radical [R] during the rearrangement of (V) to (VII). It may be that [R] has a momentary separate existence as an electrically charged carbonium ion: but Jones and Wallis [159] have suggested an alternative explanation, in which retention of asymmetry is not ascribed to an electric charge. They suppose that the univalent nitrogen atom in (V) has already begun to exercise an influence on the univalent radical

$C_6H_5 \cdot CH_2 - \overset{*}{C}H - CH_3$, before it actually parts company with the carbon atom, thus:

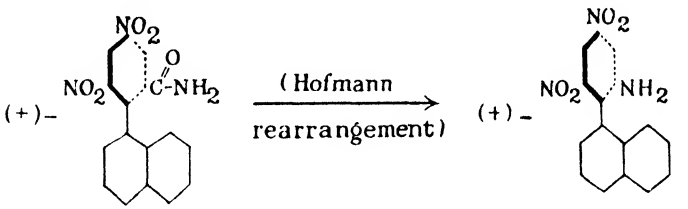
(V)



The dotted lines may be taken to represent partial valencies: and it is possible to apply a similar explanation to the above-mentioned semi-pinacolinic changes, in which case the existence of the charges K and K′ becomes an unnecessary hypothesis.[155]



Actually, a recent experiment by Wallis and Moyer [285] lends considerable support to the "partial valency" theory. When (+)-3 : 5-dinitro-6-*a*-naphthyl-benzamide (I) undergoes the Hofmann rearrangement, the resulting (+)-3 : 5-dinitro-6-*a*-naphthyl-aniline (II) is, apparently, optically pure.

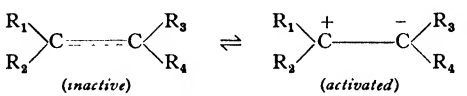


(I) (II)

This is quite to be expected, if we assume that the rearranging group, $-CO \cdot N<$, is at no time actually free from the rest of the molecule. If, on the

other hand, the $-CO \cdot N<$ group were to separate totally from the carbonium ion, even momentarily, the steric "blocking" effect of the group would vanish, free rotation of the nuclei would be possible, and total or partial racemisation would occur.

The problem of asymmetric induction remained somewhat in abeyance until the publication of Lowry and Walker's note on "Induced Asymmetry of Unsaturated Radicals in Optically Active Compounds" [161]. The view was adopted that unsaturated chromophoric groups in optically active molecules exhibit an "induced asymmetry", if coupled sufficiently closely to the centre of "fixed asymmetry". The Drude equation expressing the complex rotatory dispersion of certain optically active ketones has been found to contain one term whose dispersion parameter corresponds very closely to the ketonic absorption band: and, if we adopt the view of Lowry and Walker, such a term therefore represents the direct contribution of this chromophoric group to the rotatory power of the molecule. Reasons were also given for supposing that "polar activation" of a double bond (compare p. 99) leads ultimately to complete rupture or ionisation of one link, thus:



(inactive) *(activated)*

and that such activation, in an unsaturated optically active molecule, might lead to the production in unequal amounts of two new diastereoisomerides.

Wood and Nicholas [162], on the other hand, object that it is superfluous to regard the carbonyl group in (for example) camphor as displaying induced

asymmetry, with a view to explaining the complex rotatory dispersion of that compound. They prefer to develop the view that the two partial rotations of opposite sign, necessary to explain the complexity, can both arise at one classical asymmetric centre. A single asymmetric centre, on their theory, can give rise to two electronic components (two electronic tetrahedra), and a molecular component (a molecular tatrahedron), which can contribute partial rotations whose algebraic signs depend on the relative directions of displacement of the tetrahedra. The carbonyl group will then act rather as a deflecting and disturbing "vicinal" influence upon the electronic system, than as a true centre of asymmetry.

Various other results are recorded in the literature which may be looked upon as having a bearing on the problem of asymmetric induction, and should not be overlooked. Van 't Hoff[107], in considering the existence of optically active products in nature, predicted the possibility of their formation

> bei unsymmetrischen Versuchsbedingungen, bei Umwandlungen, z.B. die durch die Wirkung des rechts- oder links-cirkularpolarisierten Lichtes stattfinden oder durch aktive Verbindungen veranlasst werden, vielleicht sogar in aktiven Lösungsmitteln.

Asymmetric synthesis by circularly polarised light has already been discussed: and it now remains to describe the various researches which had their genesis in van 't Hoff's second suggestion.

The solubilities of two optical antipodes in an optically active solvent might be expected to differ: and several experiments on these lines have been

carried out. Tolloczo [163] dissolved *r*-mandelic acid by shaking with ether and a strong aqueous solution of fructose: while racemic acid was similarly distributed between water and (−)-amyl alcohol. In both cases, however, the acid recovered from each pair of solvents was optically inactive. Similarly, Goldschmidt and Cooper [164] found that (−)- and (+)-carvoxime had the same solubility in (+)-limonene: and Cooper [165] showed that the solubility curves for sodium-ammonium-(−)- and (+)-tartrates in dextrose solution are identical, within the limits of experimental error. Jones [166] obtained a similar result on dissolving (−)- and (+)-camphor, and (−)- and (+)-camphoroxime, in (+)-pinene and (−)-amyl bromide. More recently, Ebert and Kortüm [143] recorded similar results for the solubility of potassium-hydrogen-(−)- and (+)-tartrates in water and in aqueous mannitol, and of (−)- and (+)-camphor-sulphonic acids in benzene, and in benzene solutions of (−)- and (+)-camphor. In addition, it was found that there was no relative change in the surface tensions of aqueous solutions of sodium-(−)- and (+)-camphorsulphonates on saturating with various optically active substances, such as (−)-menthyl acetate.

The only experiment on the above lines to give any sign of success was recently announced by Schröer [167]. *r*-Mandelic acid was dissolved in (+)-carvone, and fractionally extracted with water: the acid thus obtained showed at first a slight lævorotation, which diminished progressively, passed through zero, and finally became a dextrorotation. The opposite sequence was followed when (−)-carvone was the solvent employed.

A slightly different mode of attacking this problem lies in crystallising racemic substances from optically active solvents. This method was employed by Kipping and Pope [168], who obtained an apparently positive result by crystallising sodium-ammonium-racemate from an aqueous solution of (+)-glucose. They obtained an excess of the (+)-tartrate in the crystalline crop: but the conclusion was eventually reached that this was caused by the presence of optically active crystallisation nuclei in the atmospheric dust of the laboratory [169].

A definitely positive result on these lines was, however, obtained by McKenzie [170]. He was led to attempt the resolution of racemic acid by means of (−)-malic acid, instead of by an optically active base in the usual way, by Pasteur's observation that ammonium-hydrogen-(−)-malate forms a crystalline double salt (I) with ammonium-hydrogen-(+)-tartrate, but that the corresponding compound (II) with ammonium-hydrogen-(−)-tartrate is not formed, or, at least, does not crystallise out from solution:

(I) $$\left[(+)\text{-}\begin{vmatrix} \mathrm{CH(OH)\cdot COOH} \\ \mathrm{CH(OH)\cdot COONH_4} \end{vmatrix}, (-)\text{-}\begin{vmatrix} \mathrm{CH(OH)\cdot COOH} \\ \mathrm{CH_2\cdot COONH_4} \end{vmatrix} \right]$$

(II) $$\left[(-)\text{-}\begin{vmatrix} \mathrm{CH(OH)\cdot COOH} \\ \mathrm{CH(OH)\cdot COONH_4} \end{vmatrix}, (-)\text{-}\begin{vmatrix} \mathrm{CH(OH)\cdot COOH} \\ \mathrm{CH_2\cdot COONH_4} \end{vmatrix} \right]$$

Treatment of ammonium-hydrogen-racemate with ammonium-hydrogen-(−)-malate might, therefore, have been expected to bring about resolution of the racemate, since complexes (I) and (II) are not mirror-images of one another.

Racemic acid (1 mol.) was therefore neutralised

with aqueous potash, and (−)-malic acid (1 mol.) was added. The remarkable result was observed that a crop of *dextrorotatory* crystals separated, consisting of a mixture of potassium-hydrogen-racemate and potassium-hydrogen-(+)-tartrate. In this case, the possibility that atmospheric nuclei might be the cause was eliminated by several crystallisations of the racemate, alone, with negative results. The work was also extended to the sodium, rubidium, and cæsium acid-salts, with similar results [171]: while (+)-malic acid brought about a corresponding activation of opposite sign [172]. It was found, however, that out of a series of no fewer than fifteen different optically active acids, only malic acid could effect this activation: further, while racemic acid could be activated, it was found that *r*-mandelic and *r*-dimethoxysuccinic acids showed no such effect. The author commented on this very remarkable result as follows:

> If we have to deal with a partial resolution of racemic acid, the case is interesting as providing the first example of the partial resolution of an inactive acid by an active acid instead of by an active base or alcohol. On the other hand, those chemists who are prepared to agree with Erlenmeyer in his recent ingenious claims will find in the present paper several admirable examples of "asymmetric induction" [171].

The possible directing influence of optically active solvents upon chemical reactions carried out therein has also been investigated. Boyd [110], for example, reduced benzoylformic acid in aqueous solutions of (+)-tartaric acid, or (−)-mandelic acid: but the only product was *r*-mandelic acid. Walden [173] studied the replacement of chlorine by hydroxyl in

r-monochlorosuccinic acid, in (−)-amyl-alcoholic solution: but the product was optically inactive. Kipping [32] obtained only *r*-benzoin by the action of potassium cyanide or hydrocyanic acid upon benzaldehyde, in an alcoholic solution of (+)-camphor: and the reduction of pyruvic acid in aqueous glucose led to the formation of inactive lactic acid. E. and O. Wedekind [174] studied the addition of allyl iodide to N-methyl-benzyl-aniline in (+)-limonene, (−)-menthol, and (−)-chloro-methyl-menthyl-ether: but again all results were negative.

The key to these consistently negative results is supplied by an experiment by Bredig and Balcom [175]. (+)- and (−)-camphor-carboxylic acids both decompose at the same rate into camphor and carbon dioxide, whether dissolved in (+)- or in (−)-limonene: whereas when optically active *bases* are used as solvents, such as nicotine, which undoubtedly takes part in the reaction, as a catalyst (compare p. 30), a difference between the reaction velocities for the two antipodes can be clearly demonstrated. This is comparable to Fischer's observation that there is no difference in the inversion velocities of sucrose by (−)- or by (+)-camphoric acid [176], since this velocity is proportional to the hydrogen-ion concentration of the solution, and not to the optically active anions. It would thus appear that van 't Hoff's prediction can be realised only when the optically active solvent actually has a definite chemical action upon the solute. When it merely plays the part of an inert solvent, no asymmetric inductive effect is to be expected.

It appears, then, that although the conception

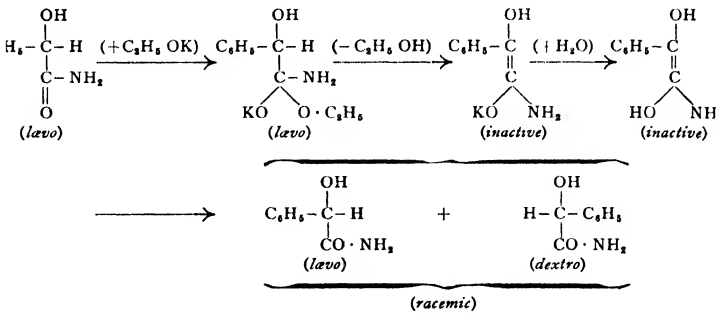
of asymmetric induction is, on the theoretical side, very valuable, and even fundamentally necessary, and although there is nothing inherently unlikely in the hypothesis, yet so far most attempts to demonstrate experimentally the existence of asymmetric induction have been fruitless. In the few cases where favourable evidence has been obtained, it is usually possible to apply an alternative explanation: a really definite and unassailable experimental proof is still lacking.

II

RECENT RESEARCHES ON THE BEARING OF ASYMMETRIC INDUCTION UPON ASYMMETRIC SYNTHESIS

DURING the past two or three years, the problem of asymmetric induction has been attacked once more by McKenzie and his co-workers, in its restricted application to the mechanism of asymmetric synthesis: and in order to understand the line of attack, we must first consider briefly McKenzie's work on *catalytic racemisation*.

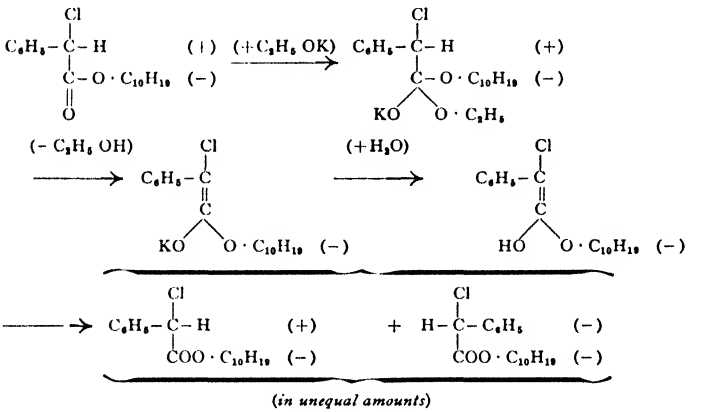
Catalytic racemisation of optically active benzoin, ethyl mandelate, or mandelamide (to quote a few examples), is readily effected in alcoholic solution by traces of alcoholic alkali. This is attributed to a temporary destruction of molecular asymmetry, by desmotropic change, which, when reversed, produces both enantiomorphs in equal amounts, with consequent loss of optical activity. Thus, in the case of mandelamide, we have:



This is described as "*symmetrical catalytic racemisation*" [177], and takes place only when a phenyl

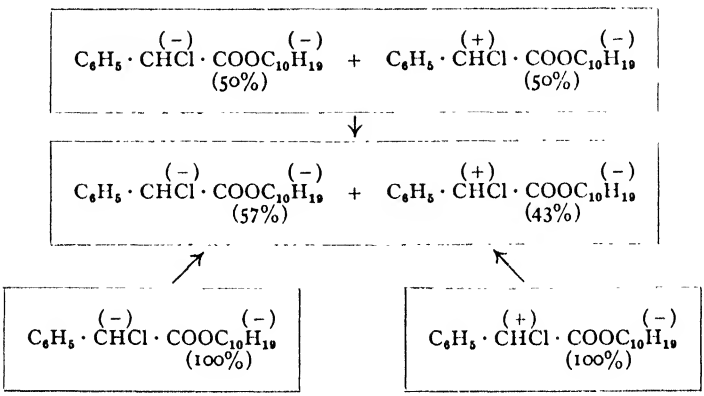
radical and a labile hydrogen atom are directly attached to the asymmetric carbon atom, in the *a*-position to a carboxyl or carbonyl group.

On extending these experiments [178, 179], it was found that addition of a trace of alcoholic potash to an ester such as (−)-menthyl-(−)-phenylchloracetate, in alcoholic solution, brought about catalytic racemisation of the optically active acid radical: but in this case the directing influence of the (−)-menthyl group, which is not itself racemised by alkali, caused the desmotropic change to proceed unsymmetrically, thus:



Hence, in this process, described as "*asymmetric catalytic racemisation*", the two diastereoisomerides in the final product are formed in unequal amounts: and it was further found that the same final equilibrium solution is obtained whether we start from (−)-menthyl-(−)-phenylchloracetate or (−)-menthyl-(+)-phenylchloracetate. Finally, following logically from this result, it was found that if we start with an alcoholic solution of (−)-menthyl-

r-phenylchloracetate, which contains both of the above diastereoisomerides in equal amounts, asymmetric catalytic racemisation alters the ratio from its initial value of unity to a different and definite value. In other words, the following scheme has been realised experimentally:



These observations were also extended, with analogous results, to the (−)-menthyl-phenylbromacetates [178], the (+)-bornyl-phenylchloracetates [179], the (−)-menthyl mandelates [179], and, more recently, to amygdalin [180].

Now, the remarkable results outlined above suggest a line of attack upon the problem of asymmetric induction. If we admit, with Erlenmeyer and with Lowry, that an unsaturated chromophoric group such as $>C=O$ may act as a labile centre of asymmetry, it seems possible that by a suitable choice of solvent and catalyst an *a*-ketonic ester, such as (−)-menthyl-benzoylformate, might be made to undergo a change of equilibrium, analogous to the above, as represented by the following scheme:

$$C_6H_5 \cdot \overset{(-)}{C}O \cdot COO_{10}\overset{(-)}{C}H_{19} + C_6H_5 \cdot \overset{(+)}{C}O \cdot COO\overset{(-)}{C}_{10}H_{19}$$

(in equal amounts)

↓

$$C_6H_5 \cdot \overset{(-)}{C}O \cdot COO\overset{(-)}{C}_{10}H_{19} + C_6H_5 \cdot \overset{(+)}{C}O \cdot COO\overset{(-)}{C}_{10}H_{19}$$

(in unequal amounts)

Further, if the velocity of transformation is not too great, such a change should be detectable polarimetrically. Keeping these considerations in mind, therefore, the rotations of six different *a*-ketonic esters of the above type were examined in various solvents by McKenzie and Mitchell [181]. Later, the observations were extended by McKenzie and Ritchie [47-49] to include seven other esters: and the collected results may be briefly summarised as follows:

(1) The *a*-ketonic acids employed were: pyruvic, benzoylformic, anisoylformic, and *a*-naphthoylformic acids. The optically active alcohols with which the above were esterified were: (−)-menthol, (−)- and (+)-borneol, (−)- and (+)-*β*-octanol.

(2) All the esters examined displayed a definite mutarotation in ethyl-alcoholic solution.* In addition, certain of the esters showed mutarotation in methyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, and (−)-amyl alcohols.

(3) In no case was mutarotation observed in non-alcoholic solvents such as benzene, acetone, or chloroform.

* With the single exception of (−)-menthyl anisoylformate. The only solvent in which mutarotation was here detected was *iso*-butyl alcohol.

(4) It was found that traces of acidic and basic catalysts increased the rate of mutarotation. The former had the more pronounced effect, and in some cases led to the almost instantaneous establishment of equilibrium [182].

(5) On allowing the alcohol to evaporate from a solution spontaneously, after the establishment of equilibrium, the ester was recovered with all its initial properties unchanged. Such a "recovered" sample of ester showed the same mutarotation phenomena when re-dissolved in the same solvent.

(6) In solvents where mutarotation was observed, the optical rotation of the pyruvates *decreased* numerically, whereas that of the other esters *increased* numerically.

(7) In certain of the solutions displaying mutarotation, a "thermal lag" was observed, analogous to that recorded by Hudson in the case of fructose and other sugars.

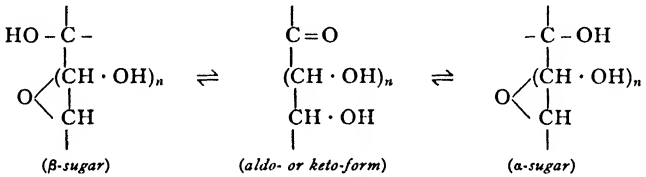
(8) The mutarotation curve for (−)-menthyl benzoylformate in ethyl alcohol was analysed, and found to obey the monomolecular law [183].

It may be noted, also, that (−)-menthyl cinnamate was examined, but was not found to display mutarotation.

Although the above experiments had been suggested by the hypothesis of asymmetric induction, it was at once realised that this was not the only basis on which the mutarotation could be explained. The observations were considered critically, in the light of various other types of mutarotation recorded in the literature, and the following conclusions were arrived at [184]:

(1) *Mutarotation due to Desmotropic Change*

A large proportion of the cases of mutarotation recorded in the literature are best explained on the basis of desmotropic change. In the case of the sugars, for example, Baker, Ingold, and Thorpe [185] have suggested the existence of an equilibrium system of the following type:*



"Keto-enol" desmotropy is also postulated as the cause of the mutarotation of (–)-menthyl acetoacetate and (–)-menthyl formylphenylacetate, observed by Lapworth and Hann [186]. A similar mechanism underlies the mutarotation of (–)-menthyl-(+)-phenylacetoacetate and (–)-menthyl-(+)-benzoylphenylacetate, recorded by Rupe and Lenzinger [187], where the initial dextrorotations change to lævorotations as the (+)-asymmetric centres are gradually destroyed by "keto-enol" change.

Now, it might be possible to apply such an explanation to the pyruvic esters under consideration, thus:

$$CH_3 \cdot CO \cdot \underset{(-)}{COOC_{10}H_{19}} \rightleftharpoons CH_2{=}C(OH) \cdot \underset{(-)}{COOC_{10}H_{19}}$$

Indeed, the "keto-enol" desmotropy of pyruvic acid itself seems to be fairly well established, on both

* Other types of reversible isomeric change have, however, been suggested, involving the intermediate formation of an aldehyde sugar or its hydrate, with intervention of water.

chemical and physical grounds [188]: while an early structural formula for pyruvic acid, put forward by Böttinger [189], suggests yet a further possibility:

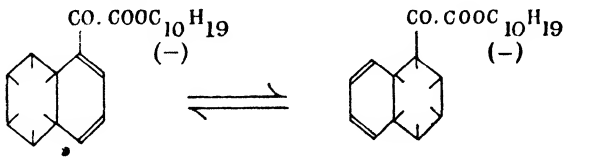
$$CH_3 \cdot CO \cdot COOC_{10}H_{19} \quad (-) \quad \rightleftharpoons \quad CH_2 - CH \cdot COOC_{10}H_{19} \quad (-)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$

It is impossible, however, to apply to the benzoylformates, anisoylformates, and α-naphthoylformates suggestions such as the above.*

(2) *Mutarotation due to Coordination Complexes*

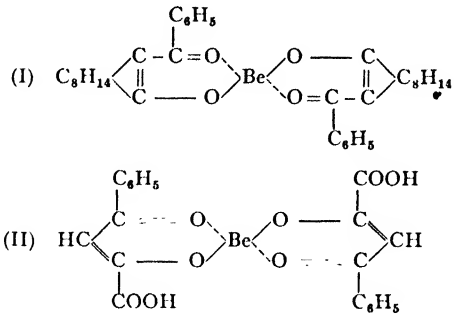
The mutarotation of benzoylcamphor [191] can be explained on the basis of desmotropic change: but the beryllium [192] and aluminium [193] salts of benzoylcamphor also display mutarotation, and here we must seek the explanation in the formation of two unsymmetrical "chelate" rings, by coordination of the central metallic atom with ketonic oxygen (I). A new labile asymmetric centre of the spiran type is thus produced, subsequent racemisation giving rise to mutarotation. This explanation has been strikingly confirmed [194] by the resolution of beryl-

* It may be noted, however, that a different type of equilibrium may be possible, between two isomeric forms of α-naphthoylformic esters. If we admit the validity of Kenyon and Pickard's explanation of the complex rotatory dispersion of methyl-α-naphthyl-carbinol [190], the following equilibrium might obtain:



(ar. form) (ac. form)

lium benzoylpyruvate (II), the antipodal forms of which display a similar mutarotation.



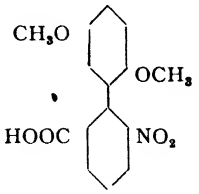
It is clear, however, that such an explanation cannot be applied to the mutarotation of optically active α-ketonic esters, though it might be possible to explain the mutarotation of the above beryllium compounds on the basis of induced asymmetry at a carbonyl group.

(3) *Mutarotation in the Diphenyl Series*

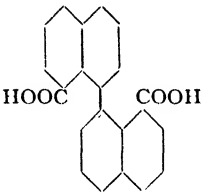
Several examples of a novel type of mutarotation have recently been described. Yuan and Adams [195] have, for example, shown that 2, 5-dimethoxy-2′-nitro-6′-carboxydiphenyl (I) is resolvable into optical antipodes, owing to restricted rotation of the two nuclei about the single bond uniting them: and the brucine or cinchonine salts of the antipodal forms have been found to display mutarotation. This is ascribed by the authors to a gradual racemisation of the unstable optically active acid radical: and other cases of the same type have since been recorded [196]. Very similar are the results recorded by Meisenheimer and Beisswenger [197] with optically

active compounds derived from 8, 8′-dicarboxy-dinaphthyl (II).

(I)



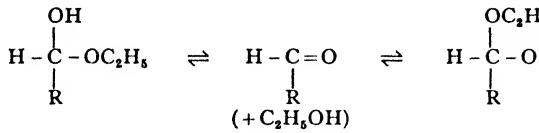
(II)



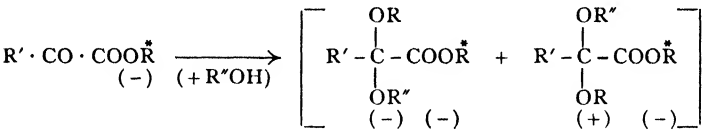
Again, however, this mechanism is inapplicable to the mutarotation under discussion.

(4) *Mutarotation due to Solvation*

The explanation of certain cases of mutarotation must lie in the gradual combination of solvent and solute. For example, alcoholic solutions of (−)- and (+)-hydroxyhydrindamine exhibit a change in rotation on standing [198]: and here no desmotropic change is possible. A solvation effect also seems most likely in the case of (+)-diphenylhydroxyethylamine, which in acetone solution displays marked mutarotation, with actual reversal of sign [199]. (−)-Benzoin-methyl-ether, $C_6H_5 \cdot CH(OCH_3) \cdot CO \cdot C_6H_5$, may also fall under this heading: for in ethyl-alcoholic solution, where solvation is not unlikely, its sign of rotation is different from that observed in inert solvents [200]. An interesting case is furnished by Wolfrom [201], who found that the crystalline alcoholate of aldehydo-galactose-penta-acetate exhibits mutarotation in chloroform solution. This he attributed to reversible decomposition of the semi-acetal into aldehyde and alcohol, and formation from these of a semi-acetal with a new configuration, thus:



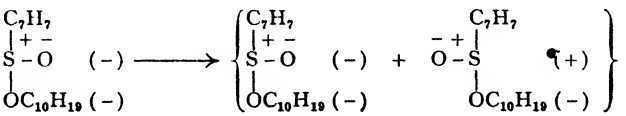
Now, some such hypothesis of alcoholic solvation can be applied to the present case of the *α*-ketonic esters. To take the most obvious case, we may suppose the following scheme to obtain:



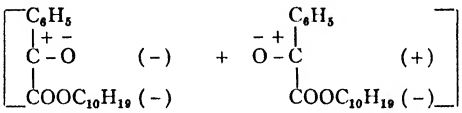
Here, the formation of the new asymmetric centre, by addition of alcohol to the *α*-carbonyl group at a measurable rate, could give rise to mutarotation. This will be discussed in detail later (p. 93).

(5) *Mutarotation due to the Presence of a Semi-polar Double Bond*

Phillips [202] has recorded mutarotation in the (−)-menthyl and (−)-*β*-octyl esters of *p*-toluene-sulphinic acid. In the same paper, optically active forms of *n*-alkyl *p*-toluene-sulphinates were described, asymmetry being due to a semi-polar double bond ($>\overset{+}{S}-\overset{-}{O}$) in the acid radical: and the above mutarotation can therefore be ascribed to gradual establishment of equilibrium between the two possible diastereoisomerides, which are presumably interconvertible, thus:

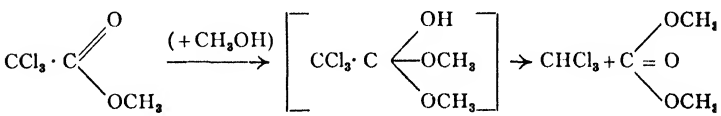


If, now, it could be shown that the *a*-carbonyl group of the *a*-ketonic esters under consideration contains a semi-polar double bond ($>\overset{+}{C}-\overset{-}{O}$), we could explain the observed mutarotation on the grounds of asymmetric induction. In the case, for example, of (−)-menthyl benzoylformate, the ester would consist of a mixture of the two possible diastereoisomerides, thus:

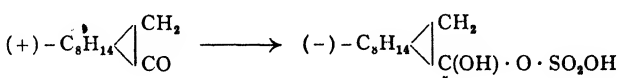


We have, therefore, to consider two possible explanations for the observed phenomena—solvation and asymmetric induction.

(A) Solvation as the Cause of the Observed Mutarotation.—The formation of a solvate-complex involving a carbonyl group has been frequently postulated in the literature to explain widely varying results. The formation of dimethyl carbonate from methyl trichloracetate, for example, is thought to follow these lines [203]:



It has been suggested, too, that the reversal of sign on dissolving (+)-camphor in sulphuric acid may be due to the formation of a ψ-salt, with production of a new asymmetric centre by solvation [204]:



Further, Herold and Wolf [205] have deduced, from measurements of optical absorption, that aldehydes in dilute alcoholic solution exist very largely as semi-acetals:

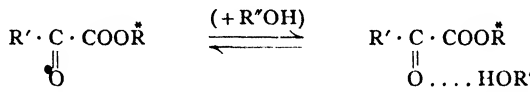
$$R \cdot CHO \underset{\leftarrow}{\overset{(+R'OH)}{\rightleftharpoons}} R \cdot CH\begin{matrix} OR' \\ OH \end{matrix}$$

Turn now to the *a*-ketonic esters under discussion. It will be observed that they can act only as donors in the formation of additive coordination compounds *—perhaps the simplest type of solvate-complex. Further, none of the solvents investigated can act as acceptors, with the exception of the alcohols (which can function either as donors or acceptors). Theoretically, therefore, solvation cannot occur by formation of a coordinate link between a molecule of ester and a molecule of (say) benzene: whereas, in the case of an alcoholic solvent, solvation can be expected to take place by means of the $>C=O$ (*ester*) and $-OH$ (*solvent*) radicals. These considerations fit in with the observed absence of mutarotation in non-alcoholic solvents: but they suggest no adequate reason for the fact that in secondary and tertiary alcohols no mutarotation has so far been observed (with the single exception of (−)-menthyl pyruvate in *iso*-propyl-alcoholic

* The formation of addition complexes between quinones and amines, etc., has been attributed by Meyer [206] to the ketonic oxygen atoms in the quinone molecule. But as Bennett and Willis [207] have pointed out, amines are donors; and the ketonic oxygen atoms cannot accept electrons unless $>C=O$ becomes activated, in some way, to $>\overset{+}{C}-\overset{-}{O}$. If this semi-polar double bond is formed, union with the tertiary base takes place thus:

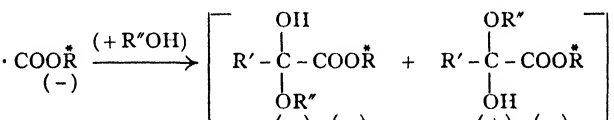
$$>C\begin{matrix} \overset{-}{O} \\ \overset{+}{N}R_3 \end{matrix}$$

solution). Nevertheless, it is possible to explain the observed mutarotation by the gradual establishment of the following type of equilibrium:



It should be noted that no new asymmetric centre is created here: neither is it necessary to assume that the whole of the ester is combined with solvent at the equilibrium point.

As pointed out in a previous paragraph, however, solvation can also occur, theoretically, by mechanisms not involving a coordinate link. The following scheme depicts another alternative explanation, already outlined briefly on p. 90:



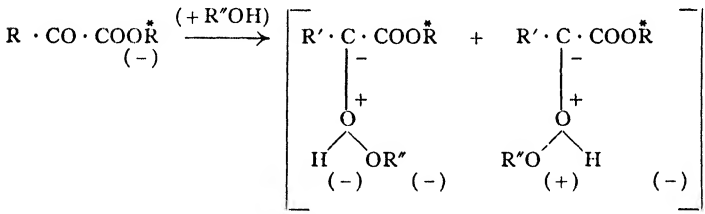
In this case, by semi-acetal formation, a new asymmetric centre is generated: and it is possible to explain the observed mutarotation by the gradual addition of solvent to the *a*-carbonyl group, under the directing influence of the optically active radical $\dot{R}$, with consequent production of the two possible diastereoisomerides. Three modifications of this scheme suggest themselves, as follows:

(i) It is possible that solvation occurs almost instantaneously on solution, with production of *both* diastereoisomerides in *equal* amounts: adjustment of equilibrium between the two forms, giving rise to *unequal* amounts, would then cause mutarotation.

(ii) It is also possible that such an instantaneous solvation would generate only *one* of the two isomers: partial transformation into the other form would then give rise to mutarotation (on the lines suggested by Phillips for the (−)-menthyl and (−)-β-octyl *p*-toluene-sulphinates, as described on p. 90).

(iii) Finally, even if the two diastereoisomerides were finally produced in *equal* amounts by solvation —not a very likely occurrence—mutarotation would be observed if this semi-acetal formation were gradual, not instantaneous.

Still another possible solvation mechanism is suggested in the following scheme:



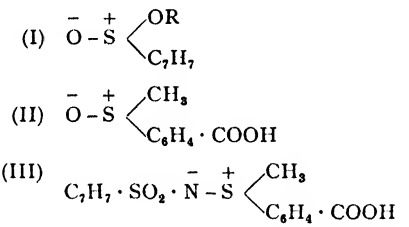
Here, as in the case first considered, addition of solvent takes place at the α-ketonic oxygen atom—this time, however, not by a single coordinate link, but by the addition of two separate ions by ordinary covalencies. It will be seen later, when we come to consider the electronic structure of the C = O group, that this necessitates the formation of a semi-polar double bond between carbon and oxygen, as shown above: and a new asymmetric centre will thus be formed. Gradual establishment of equilibrium between two diastereoisomerides of the three general types detailed in the previous paragraph, once again provides a possible cause of mutarotation. In this

case, the initial solvation gives rise to a true case of asymmetric induction.

It will be seen from the foregoing that the hypothesis of solvation provides several almost equally likely alternative explanations for the mutarotation of optically active *α*-ketonic esters in alcoholic solution. These will not be considered further, except to point out that all the solvent-solvate complexes suggested above are almost certainly of a very low degree of stability [208]: we would expect, therefore, that spontaneous evaporation would result in the total elimination of solvent and regeneration of the ester in its original form—a result actually obtained in practice. (See Section (5), p. 85.)

(B) ASYMMETRIC INDUCTION AS THE CAUSE OF THE OBSERVED MUTAROTATION.—As has already been stated, no mutarotation has so far been observed in non-alcoholic solvents: and this would appear to be *prima facie* evidence for the hypothesis of alcoholic solvation. It does not, however, exclude the alternative explanation on the basis of asymmetric induction: for the absence of mutarotation in any particular solvent may simply mean that the hypothetical equilibrium, which is established at a measurable rate in (say) ethyl alcohol, is in this case reached almost instantaneously. This may be ascribed to the accidental presence of an unknown catalyst: but it is much more convincing to attribute the effect to the more marked "*adjuvance*" of non-mutarotating solvents, such as acetone. The work of Norris and Prentiss [209] on the "*adjuvance*" of various alcohols does, in fact, suggest a reason for the fairly general failure to detect mutarotation in methyl-alcoholic solutions.

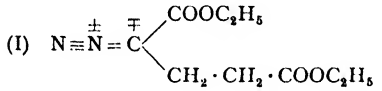
It has already been shown (p. 91) that the mutarotation in question can be explained by the development of induced asymmetry at the *a*-carbonyl group of the esters examined. The most likely mechanism of such an asymmetric induction lies in the formation of a semi-polar double bond in the *a*-carbonyl group: for there can be no doubt that this could give rise to a new centre of asymmetry. The existence of optically active molecules with only *three* radicals attached to the central asymmetric atom has been definitely proved by Phillips and Kenyon [210], who have resolved certain sulphinic esters (I), unsymmetrical sulphoxides (II), and the sulphonylimines (III) described by Pope and Mann [211].



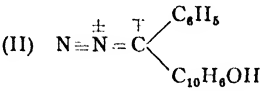
In all these cases, the existence of antipodal molecules is explained by the formation of a semi-polar double bond,* as indicated above, although the double bonds of the older structural formulæ indicated no possibility of asymmetry. In a similar way, the existence of aliphatic diazo-compounds in an optically active form has been explained by the presence of one or more semi-polar double bonds. It should be noted, in this connection, that the evidence adduced by Chiles and Noyes [213], and Levene and Mikeska [214], for the existence of an optically

* Note, however, the explanation advanced by Bergmann and Tschudnowsky [212]. See p. 101.

active ethyl-*a*-diazo-glutarate (I) has recently been shown to be unreliable by Weissberger and co-workers [215]. Nevertheless, the existence of such compounds has been definitely confirmed by Ray [216], who prepared crystalline, highly active (+)- and (−)-*β*-naphthol-phenyl-diazomethane (II) by diazotising the active forms of *β*-naphthol-phenyl-amino-methane.



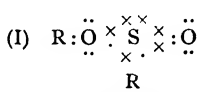
(I) $N\overset{\pm}{=}\overset{\mp}{N}=C\begin{matrix}\diagup\ COOC_2H_5\\ \diagdown\ CH_2\cdot CH_2\cdot COOC_2H_5\end{matrix}$



(II) $N\overset{\pm}{=}\overset{\mp}{N}=C\begin{matrix}\diagup\ C_6H_5\\ \diagdown\ C_{10}H_6OH\end{matrix}$

Similarly, if it could be established that semi-polar double bonds can be formed in carbonyl and ethylenic groups, it could be stated definitely that compounds such as the *a*-ketonic esters described in these investigations, or the cinnamic acids described by Erlenmeyer, could develop asymmetric centres not foreseen by classical theory.

It is found, however, that according to accepted modern electronic theories, the two sets of cases are not strictly parallel. Consider, first, the sulphinates, sulphoxides, and sulphonylimines quoted above. The electronic formula of a sulphinate of the type in question may be written in two possible ways:



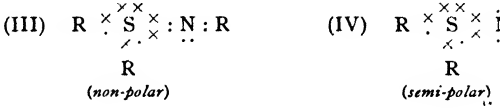
(I) $R:\ddot{O}\times\overset{\times\times}{\underset{\times\cdot}{S}}\times:\ddot{O}$ (II) $R:\ddot{O}\times\overset{\times\times}{\underset{\times\cdot}{S}}\times\ddot{O}:$

R R

(non-polar) *(semi-polar)*

—where × indicates an electron derived from the sheath of the central sulphur atom S, and · an electron from the sheath of one of the attached atoms. Almost identical formulæ may be written for the

sulphoxides, while the sulphonylimines may be represented thus:



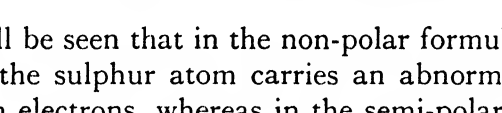
(III) (non-polar) (IV) (semi-polar)

Now, Sugden, Reed, and Wilkins [217], by means of parachor measurements, have adduced strong evidence that—

> semi-polar double bonds are formed only when each atom, except hydrogen, has attained a complete octet. The octet is never exceeded, and semi-polar bonds are not found when their existence necessitates the presence of a sextet around one or other of the atoms concerned. . . .

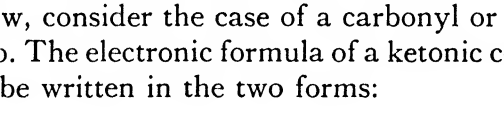
It will be seen that in the non-polar formulæ (I and III) the sulphur atom carries an abnormal sheath of ten electrons, whereas in the semi-polar formulæ (II and IV) it carries only a normal octet. Hence, on both theoretical and experimental grounds, the latter formulæ are taken to be correct.

Now, consider the case of a carbonyl or ethylenic group. The electronic formula of a ketonic compound may be written in the two forms:



(V) (non-polar) (VI) (semi-polar)

—and that of an ethylenic compound in the two forms:



(VII) (VIII)

In the non-polar formulæ (V and VII), all the carbon atoms bear a normal octet: while in the semi-

polar formulæ (VI and VIII) this is reduced to an abnormal sextet. Hence, we are led to the conclusion that only in abnormal circumstances will the formation of a semi-polar double bond be possible in a carbonyl or ethylenic grouping. Actual parachor measurements of a large number of compounds containing these groups, and including (−)-menthyl benzoylformate [181], confirm this conclusion.

Lowry and Owen [218] have, however, concluded that "polar activation" of a ketonic group can occur under certain activating influences, such as absorption of light by the carbon valency electrons, two of which will be progressively displaced towards the oxygen atom. Carried beyond a certain limit, this process would end in the ionisation of one link of the double bond, thus producing a semi-polar double-bond. (Compare p. 74.)

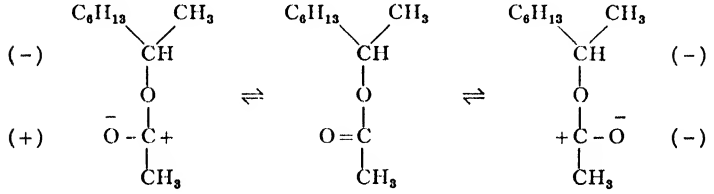
$$>C=O \rightleftharpoons >\overset{+}{C}-\overset{-}{O}$$

In a similar way, Eastman [219] concludes that under certain conditions an ethylenic linking, which normally occurs as a non-polar double bond, may assume the semi-polar form shown in formula VIII, one of the carbon atoms utilising the two electrons from its inner orbit to fill the spaces in its depleted sheath.

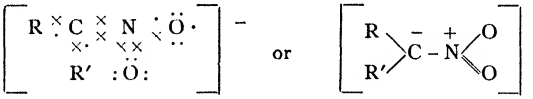
Further, Lowry and Cutter [220] consider that "the complex [rotatory] dispersion, which so often appears in passing from an optically active alcohol to its esters, may be due to the development of a partial rotation of opposite sign in the carbonyl radical of the unsymmetrical molecule, just as in the case of camphor".

Developing this idea, Phillips [202] has put forward

the very similar suggestion that the complex rotatory dispersion displayed by carboxylic esters of optically active secondary alcohols might be due to the presence within the apparently homogeneous ester of two isodynamic forms, possessing rotations of opposite sign and different dispersive powers. It was suggested that these forms might arise through the formation of a semi-polar double bond in the carboxylic carbonyl group: thus, (−)-β-octyl acetate could be represented as the following equilibrium system: *



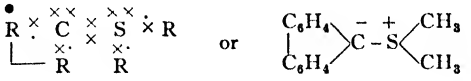
The existence of a semi-polar bond involving a carbon atom has been rendered very probable by the work of Kuhn and Albrecht [221], who showed that when (+)-β-nitrobutane is converted into its sodium salt the optical activity does not disappear. Shriner and Young [222] observed the same phenomenon with (+)- and (−)-β-nitro-octane (see also p. 28): and the most probable explanation of these results lies in the formation of the following active ion from the *aci*-form of the nitro-paraffin:



Further, the isolation of dimethylsulphonium-

* The two new forms are diastereoisomeric, and not, as Phillips states, enantiomorphous.

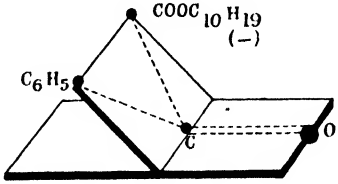
fluorenylidide by Ingold and Jessop [223] provides a case of a semi-polar double bond between carbon and sulphur, and strengthens the case for the analogous nitrogen compound mentioned above:



The formation of a similar semi-polar double bond in a carbonyl group should not, therefore, be considered definitely impossible: though, from the purely theoretical standpoint, it has been seen that such a bond will probably not occur under normal conditions. On the other hand, its formation would provide a simple explanation of the complex rotatory dispersion of certain optically active ketonic compounds; in fact, Lowry and Cutter [220] were unable to explain the dispersion of camphor and its derivatives on any other basis, though this view has been challenged by Wood and Nicholas [162].

The assumption of a dissymmetrical environment by a carbonyl group is most readily explained, as outlined above, by the formation of a semi-polar double bond: but it should not be overlooked that this is not the only possible mechanism. Bergmann and Tschudnowsky [212] have concluded, from measurements of dipole moment, that the oxygen atom in a sulphoxide does not lie in the same plane as the sulphur atom and the two other radicals attached thereto. They state, in fact, that the existence of a semi-polar double bond need not be postulated in order to explain the optical activity of Phillip's sulphoxides: simple displacement of the oxygen atom from the plane of the other three

groups is sufficient to render the molecule unsymmetrical. On this view, we may picture the molecule of (−)-menthyl benzoylformate as existing in some such non-planar form as the following:

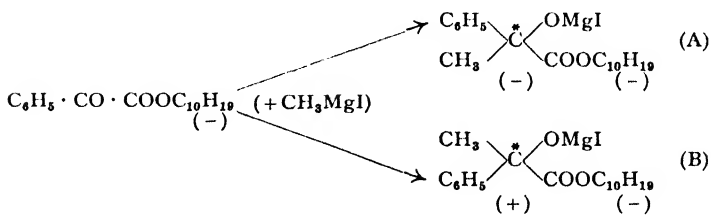


An unbiassed survey of the above arguments shows that it is extremely difficult to decide whether the mutarotation of optically active *a*-ketonic esters should be attributed to a solvation effect, or to asymmetric induction. Obviously, more evidence is required before the correctness of the conception of asymmetric induction can be definitely accepted or rejected. The solvation hypothesis has certainly the merit of simplicity: on the other hand, it will be shown in the following section that certain remarkable predictions can be made, based on the conception of asymmetric induction, which could not be made on the alternative hypothesis. It is submitted that the following results offer an argument in favour of the hypothesis of asymmetric induction which should not be overlooked.

III

AN INTERPRETATION OF McKENZIE'S ASYMMETRIC SYNTHESES, ON THE BASIS OF ASYMMETRIC INDUCTION

AT the time when McKenzie's first asymmetric syntheses by the Grignard reaction were carried out (see pp. 22-23), the apparently haphazard variation in sign of rotation of the resulting optically active acids was not made the basis of any speculation as to the underlying reaction-mechanism. The syntheses were explained on the very reasonable assumption that the optically active alcoholic radical exerted a directing influence (not very precisely defined) upon the addition of the Grignard reagent to the unsaturated *a*-carbonyl group of the ester. This influence led to the result that, prior to the final hydrolysis, unequal amounts of the two possible diastereoisomeric esters were present in the mixture. Thus, in the first asymmetric synthesis of (-)-atrolactinic acid, it was assumed that the following stage in the reaction—

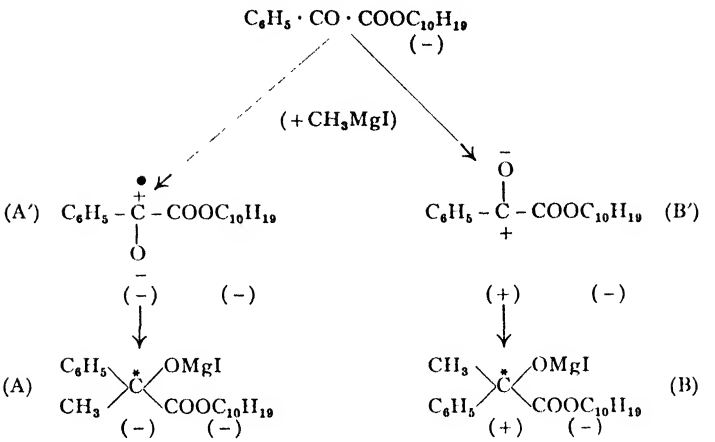


took place in such a way that there was an excess of A over B, so that on decomposition of the above products with water, followed by complete hydro-

lysis and removal of menthol, a mixture of (−)- and *r*-atrolactinic acids was obtained. In addition, it was suggested that the actual excess of A over B depended upon the numerical magnitude of the optical rotation of the alcoholic radical used as the directing influence: and this was apparently confirmed by the comparatively slight extent of the asymmetric synthesis carried out with (−)-bornyl, and with (+)-amyl, benzoylformate.

Further than this, however, the theory of the reaction mechanism was not carried. The precise nature of the postulated directing influence was not defined: nor was any attempt made to account for, or predict, the sign of rotation of the acid obtained from any particular synthesis.

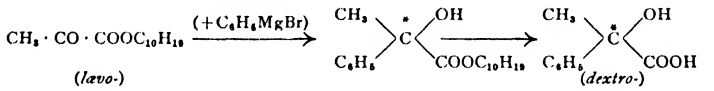
Let us now, in the light of the hypothesis of asymmetric induction, follow out in some detail the mechanism of such an asymmetric synthesis. For example, in the asymmetric synthesis of (−)-atrolactinic acid quoted above, the actual addition of solvent (ether, in this case) to the ester is assumed to give rise to *unequal* amounts of the two possible diastereoisomerides, A′ and B′, in each of which the *a*-carbonyl group is now in a definite asymmetric configuration before the actual addition of the Grignard reagent takes place. *Unequal* amounts of A and B will therefore be formed, with A in excess, as was deduced long ago from the earlier results:



The configuration adopted by the *a*-carbonyl group in A′ and B′ will be retained in A and B, and also in the (−)- and (+)-atrolactinic acids finally produced (with the former in excess). Thus, it is possible to formulate on these lines a fairly precise conception of the nature of the directing influence previously postulated.

Consider, now, the mutarotation displayed by optically active *a*-ketonic esters in alcoholic solution. (−)-Menthyl benzoylformate, for example, shows a gradual numerical *increase* in rotation, on standing. From the standpoint of asymmetric induction, this would appear to mean that in the solution the *a*-carbonyl groups are assuming a dissymmetric configuration, with the lævorotatory antipode in excess, thus adding a *lævo partial rotation* to the initial lævorotation of the ester (due only to the (−)-menthyl group), in accordance with the conception of optical superposition. This would lead us to expect that in the asymmetric synthesis mentioned above, the lævorotation initiated at the

a-carbonyl group would be propagated, through the intermediate Grignard complex, to the final product, atrolactinic acid: and this was actually observed. Similarly, (−)-menthyl pyruvate, which exhibits a gradual *decrease* in lævorotation in alcoholic solvents, is considered to develop an excess of dextro- over lævo-rotation in the *a*-carbonyl asymmetric centre. This leads us to predict the formation of a (+)-atrolactinic acid on treating this ester with phenyl magnesium bromide: and this again has actually been observed:



Comparing the essential points of the above argument with the views expressed by Erlenmeyer on asymmetric synthesis and asymmetric induction, it will be seen that the two conceptions are substantially identical.

At the time when it was put forward, it was, of course, realised that this idea was speculative in the extreme, and subject to certain serious objections. It could not, for example, be rigorously upheld that a configuration which would produce a (say) lævo-partial rotation at the *a*-carbonyl "induced" asymmetric centre would necessarily, when propagated to the optically active acid finally formed, give rise to an optical rotation of the same sign. In most cases, doubtless, this would follow: but, to be able to say that it follows in every case, we would require a fuller knowledge of the relation between configuration and sign of optical rotation than we at present possess. Further, we have assumed that a change in equilibrium actually occurs in ethereal solution,

prior to addition of the Grignard reagent, though in actual practice the mutarotation which we have associated with such a change has been detected only in alcoholic solutions. Finally, the mutarotation can equally well be explained by various solvation mechanisms. Nevertheless, the conception of asymmetric induction, as applied by McKenzie and Mitchell, offered such a neat interpretation of the older work on asymmetric synthesis that further investigation was obviously desirable.

The question which had to be settled may be formulated as follows: Is it legitimate to predict that an optically active *α*-ketonic ester, whose rotation in alcoholic solution shows a numerical *increase* on keeping, will give rise to a substituted glycollic acid *with the same sign of rotation as the parent ester*, when acted upon by a Grignard reagent? In a similar way, if its rotation *decreases* on standing in alcoholic solution, are we justified in predicting that the asymmetric synthesis will give rise to an acid having a rotation *of the opposite sign to that of the parent ester*?

At the time when this question was formulated, there were available for consideration data from nineteen * previous asymmetric syntheses of this type, carried out by McKenzie and his co-workers. Since then, eleven additional syntheses have been carried out by McKenzie and Ritchie, introducing new types of *α*-ketonic ester. Thirty distinct cases, of very varied types, are now available, therefore, in which the result of the asymmetric synthesis can be compared with the mutarotation of the parent

* The four syntheses from amyl esters [45] are omitted from these considerations, since no mutarotation data are available as a basis for prediction in the case of these compounds.

ester. For ease of reference, these results are tabulated below:*

TABLE I

Ester.	Direction of Muta-rotation.	Grignard Reagent employed.		Sign of Rotation of substituted Glycollic Acids formed.	
				Predicted.	Observed.
MENTHYL ESTERS					
(−)-Menthyl benzoylformate	⟶	CH_3MgI	40, 43	−	−
		C_2H_5MgBr	40	−	−
		n-C_3H_7MgI	43	−	−
		iso-C_4H_9MgI	43	−	−
		teri-C_4H_9MgI	43	−	−
		α-$C_{10}H_7MgBr$	43	−	−
(−)-Menthyl anisoylformate	⟶	CH_3MgI	48	−	−
		C_6H_5MgBr	224	−	−
(−)-Menthyl pyruvate	⟵	C_2H_5MgBr	43	+	+
		C_6H_5MgBr	43	+	+
		iso-C_4H_9MgI	44	+	+
		α-$C_{10}H_7MgBr$	44	+	+
		p-$CH_3O \cdot C_6H_4MgBr$	48	+	+
(−)-Menthyl *a*-naphthoyl-formate	⟶	CH_3MgI	49	−	−
		C_2H_5MgBr	49	−	−
		C_6H_5MgBr	49	−	−
BORNYL ESTERS					
(−)-Bornyl benzoylformate	⟶	CH_3MgI	43	−	−
		C_2H_5MgI	43	−	−
		iso-C_4H_9MgI	43, 225	−	−(?)
		α-$C_{10}H_7MgBr$	43	−	[+]
(+)-Bornyl benzoylformate	⟶	C_2H_5MgI	181	+	+
(−)-Bornyl pyruvate	⟵	C_2H_5MgBr	44	+	+
		C_6H_5MgBr	44	+	+
		iso-C_4H_9MgI	44	+	+
		α-$C_{10}H_7MgBr$	44	+	[−]
(−)-Bornyl *a*-naphthoyl-formate	⟶	CH_3MgI	49	−	−

* The symbol ⟶, used in the tables, indicates that the rotation in alcoholic solution (whether dextro or lævo in sign) *increased* numerically on standing. The symbol ⟵ indicates that the rotation *decreased.*

TABLE I—*continued*

Ester.	Direction of Muta-rotation.	Grignard reagent employed.		Sign of Rotation of substituted Glycollic Acids formed.	
				Predicted.	Observed.
β-Octyl Esters					
(−)-*β*-Octyl benzoylformate	→	CH_3MgI	47	−	−
(+)-*β*-Octyl benzoylformate	→	α-$C_{10}H_7MgBr$	47	+	[−]
(−)-*β*-Octyl pyruvate	←	C_6H_5MgBr	47	+	+
(+)-*β*-Octyl pyruvate	←	α-$C_{10}H_7MgBr$	47	−	−

It will be seen that among the (−)-menthyl esters there is not a single exception to the predictions made from the mutarotation data. When we turn to the syntheses carried out starting from (−)- and (+)-bornyl and (−)- and (+)-*β*-octyl esters, four anomalous cases present themselves. These have all been carefully examined and repeated. In three cases, the original anomalous result was confirmed: and it may, perhaps, be significant that these all involve the same Grignard reagent—*α*-naphthyl magnesium bromide. (It should, however, be noted that the remaining three syntheses involving this reagent all gave the predicted result.) In the fourth exceptional case—the action of *iso*-butyl magnesium iodide upon (−)-bornyl benzoylformate—McKenzie originally obtained a dextrorotatory product. This synthesis has since been repeated twice, by the present writer [225]: but in both cases the product now

showed a slight lævorotation.* The result of this particular synthesis is, therefore, somewhat indefinite. Even so, it will be seen from the previously tabulated results that out of *thirty* different asymmetric syntheses of this type, no fewer than *twenty-six* definitely bear out the predictions made on the basis of asymmetric induction. The exceptional cases in the table are marked with brackets, thus: [ ]

If we are content to explain the mutarotation of the parent esters on the orthodox and obvious basis of solvation, no predictions such as the above are possible: and the precise mechanism of these asymmetric syntheses remains, as before, rather obscure. In a large majority of cases, however, the predictions made on the boldly speculative basis of asymmetric induction were experimentally confirmed: and it is therefore submitted that the mechanism of asymmetric synthesis elaborated on this novel basis in the preceding pages has considerable experimental evidence in its favour. The writer would like to emphasise once again that the hypothesis of asymmetric induction is here advanced only ten-

* In one of his earlier papers on asymmetric synthesis, McKenzie [45] commented as follows upon the variation in *magnitude* of rotatory power observed in the optically active products: "All the evidence which has been accumulated up to this point undoubtedly points to the conclusion that the more optically active is the directing asymmetric agent the more pronounced is the asymmetric synthesis". This idea, however, was not confirmed by the present writer. The extent of any asymmetric synthesis of this type appears to depend as much upon the conditions obtaining during the Grignard reaction as upon the rotatory power of the directing system: on repeating such a synthesis several times, the activity of the product has been found to vary markedly. The case recorded above is, however, the only one in which there is the least doubt about the *sign* of rotation—a rather puzzling result.

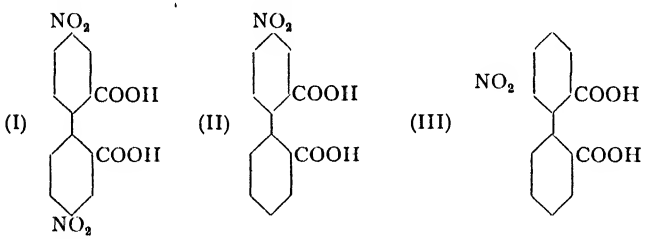
tatively, and with very considerable reserve: but it constitutes a definite advance in our views on asymmetric synthesis, and, as an incentive to further research, it must be regarded as neither superfluous nor useless.

IV

EVIDENCE FOR THE EXISTENCE OF INDUCED ASYMMETRY IN THE DIPHENYL SERIES

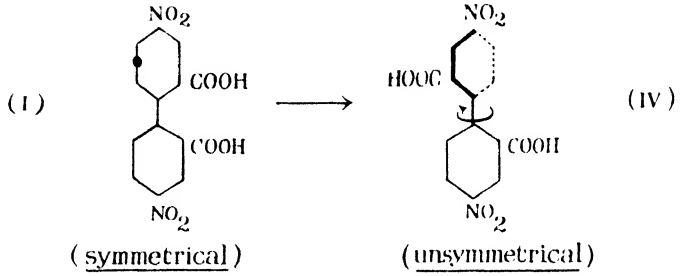
IT now remains for us to review a novel series of results, not previously considered, which may be considered to lend some support to the theory of asymmetric induction.

In 1927, Kuhn and Albrecht [226] had occasion to convert 4 : 4′-dinitrodiphenic acid (I) into its quinine salt. The surprising result was observed



that the apparently homogeneous product, amounting to 80 per cent of the theoretical yield, was strongly *dextrorotatory*, showing $[a]_D^{22} + 110°$ in chloroform solution. A similar result was recorded for cinchonidine: whereas the corresponding salts of phthalic and *m*-nitrobenzoic acids, which bear a certain structural relationship to (I), exhibited merely normal lævorotations. The authors attributed this result to the development of asymmetry in the diphenyl molecule, similar to that described by Christie and Kenner [227]. The directing influence of the alkaloid was supposed to induce the acidic portion of the salt molecule to adopt an asymmetric

configuration, such as (IV), by rotation of one nucleus, relative to the other, about the single bond uniting them:



Kuhn and Albrecht calculated that the free acid should show $[a]_D^{22} + 700°$, though they found that in actual practice only *inactive* acids could be liberated from the alkaloidal salts. This result presumably arises through the immediate destruction of this novel asymmetry on removal of the alkaloid, which has acted as the directing influence in the temporary "asymmetric transformation". The acid in question is insufficiently *ortho*-substituted to retain a permanent and stable independent asymmetry.*

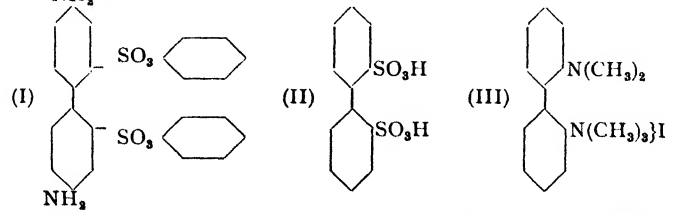
One or two other cases have since been recorded in the diphenyl series which appear to be comparable to the results of Kuhn and Albrecht. The quinine salt of 4-nitrodiphenic acid (II), for example, has been found by Bell and Robinson [231] to be *dextrorotatory*: but, although successive crystallisations

* It has been stated that at least *three* of the four *ortho*-positions (2 : 2′ : 6 : 6′) must be substituted before free rotation of the nuclei can be inhibited. Recently, however, Turner and his collaborators have succeeded in resolving phenyl benzidine-2 : 2′-disulphonate (I) [228], diphenyl-2 : 2′-disulphonic acid (II) [229], and *o*-(dimethylaminophenyl) phenyltrimethylammonium iodide (III) [230]. These are simply special cases of the above rule: for the 2 : 2′ substituents are here

altered the magnitude of its rotatory power, only an inactive acid could be obtained from the salt, as the diphenyl radical is again insufficiently substituted to maintain a stable asymmetry. Further, these authors resolved 6-nitrodiphenic acid (III) into optical antipodes, showing $[a]_{5461} \pm 66°$ (approx.) in ethyl-alcoholic solution. In caustic soda solution, however, reversal of sign was noted, with very great numerical increase in rotatory power: rotations of no less than $[a]_{5461} \mp 434°$ (approx.) were now observed. More recently, Lesslie and Turner [232] have intimated that quinine diphenate is strongly *dextrorotatory*, and exhibits mutarotation. In this connection, Turner [232] is of the opinion that Kuhn's effect should be shown by any substituted diphenic acid which is incapable of maintaining a stable dissymmetric configuration.

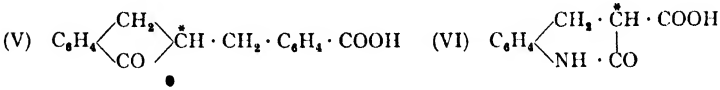
The above results may be instructively compared to an interesting group of results which have been termed "asymmetric transformations" [233]. Perhaps the most illuminating, though not the first to be recorded, are the results of Leuchs. He attempted to resolve β-(benzyl-*o*-carboxylic acid)-*a*-hydrindone

sufficiently large to be obstructed by the 6 : 6′ hydrogen atoms. The latter act just like the larger substituents (NO_2 or COOH) in earlier experiments.



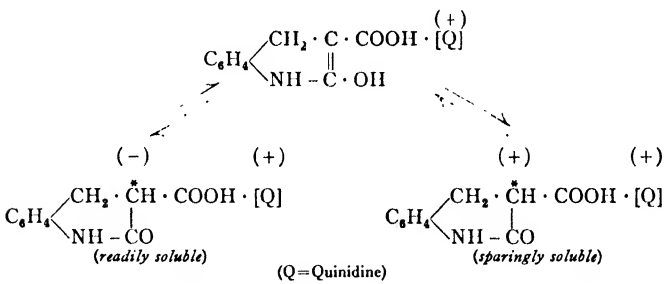
Similar cases have also been recorded by Corbellini and Pizzi [282], and Searle and Adams [283].

(V) by means of brucine [234], and hydrocarbostyril-β-carboxylic acid (VI) by means of quinidine [235]:



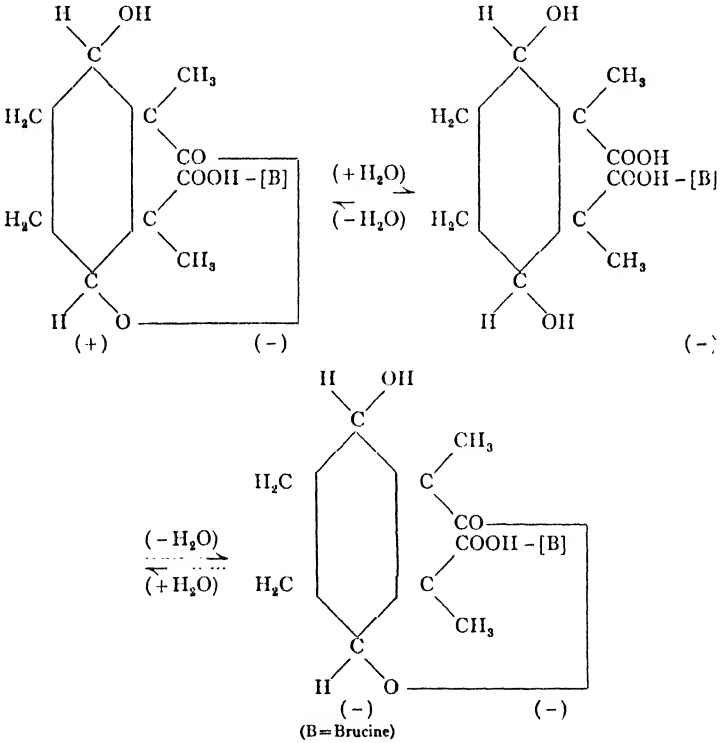
but in each case the attempt led to the complete conversion of the *r*-acid into its (+)-antipode. This, on liberation from the alkaloidal salt, was wholly autoracemised by keto-enol change involving the asymmetric carbon atom.

These "asymmetric transformations" have an ingenious and convincing explanation. In the case, for example, of hydrocarbostyril-β-carboxylic acid (VI), the sparingly soluble (+)-quinidine-(+)-acid complex crystallises out first: but the residual excess of the (+)-quinidine-(−)-acid complex, in the mother liquor, cannot be isolated, as it is rapidly reconverted into an equimolecular mixture of the two diastereoisomeric salts, by re-establishment of the following keto-enol equilibrium:



As the sparingly soluble salt gradually crystallises out, therefore, the equilibrium is progressively displaced (in the above representation) towards the right, until finally no (+)-quinidine-(−)-acid complex remains.

Very similar is the result recorded by Gadamer [236], who found that *r*-cantharolic acid is completely activated to the (−)-antipode on attempting to resolve the acid with brucine. Here, however, the autoracemisation is effected in the mother liquors by means of a hydrolysis-equilibrium between the acid, which is an unsymmetrical lactone, and its symmetrical hydrate, thus:

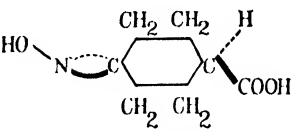


A parallel activation of *r*-*a*-cyanopropionic acid by means of cinchonine has been observed by Ahlberg [237].

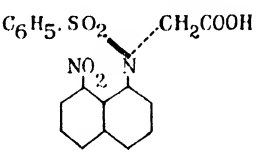
Autoracemisation of the more soluble alkaloidal

salt, in the mother-liquors, has also been advanced as an explanation of analogous results obtained in other fields. Werner [238], for example, found that attempts to resolve potassium dihydrogen tri-oxalato-chromiate, $[Cr(C_2O_4)_3]KH_2$, by means of strychnine, simply transformed the inactive complex salt into one of the two possible antipodal forms: and Mills and Bain [239] had the same experience in preparing the optically active modifications of the oxime of *cyclo*hexanone-4-carboxylic acid (VII) by means of morphine and quinine. They made the comment that "the process therefore appears to be one of activation rather than of simple resolution and recalls the behaviour of the methylethylpropyl tin *d*-camphor sulphonate and bromocamphorsulphonate described by Pope and Peachey" [240].

(VII)



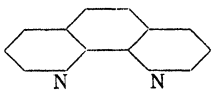
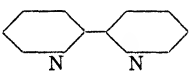
(VIII)



The same process appears to be at work in the activation of N-benzenesulphonyl-8-nitro-1-naphthyl-glycine (VIII) by means of brucine, recorded by Mills and Elliott [241]. Similarly, Read and McMath [242], in describing their preparation of optically active chloro-bromo-methane-sulphonic acid and chloro-bromo-acetic acid by means of active hydroxy-hydrindamine, put forward the opinion that such compounds, under the influence

of optically active bases, "will be transformed more or less completely into one of the two possible active modifications: but when the asymmetric influence is removed, the form present in excess will undergo auto-racemisation".

In 1931, Pfeiffer and Quehl [243] observed a novel optical effect in solutions of certain optically active substances, which appears to fall into the same category as the foregoing. They found that the addition of three molecules of *a*-phenanthrolene (IX) to aqueous solutions of zinc *β*-camphorsulphonate, or of zinc *a*-brom-*π*-camphorsulphonate, caused a marked diminution, or increase, respectively, of specific rotatory power. With zinc quinate, a similar effect, though of smaller magnitude, was observed.

(IX)  (X) 

It was found, too, that *a*, *a*-dipyridyl (X) behaved similarly to *a*-phenanthrolene in the above cases, though less pronouncedly: other bases examined were, however, quite ineffective. The authors attributed these optical effects to the formation in solution of new asymmetric centres. Presumably, tridipyridyl- and triphenanthrolene-zinc ions, $[Zn(dip)_3]^{++}$ and $[Zn(phen)_3]^{++}$, are formed, in which the zinc atom is optically active owing to the asymmetric octahedral configuration of the basic molecules. The rotatory power of these ions, however, disappears on removing the optically active camphorsulphonic grouping: for example, the active salt $[Zn(phen)_3](O \cdot SO_2 \cdot C_{10}H_{15}O)_2, 7H_2O$ yields the inactive salt $[Zn(phen)_3]Br_2, 7H_2O$, on treatment with potassium bromide.

It was further observed that the addition of three molecules of *a*-phenanthrolene to an equimolecular solution of zinc sulphate and cinchonine hydrochloride (or strychnine sulphate) gave a marked decrease in rotatory power: hence, optical activity can be induced in the complex ion $[Zn(phen)_3]^{++}$ either by negative active acid ions or by positive active alkaloid ions. That the above effects are perfectly general has since been demonstrated by the observation that other metals, such as cadmium, nickel, cobalt, and manganese, display similar effects [244].

The close analogy between these results, and those previously recorded in the diphenyl series, was first pointed out by Kuhn [245]. He put forward the proposal that the term "asymmetric transformation of the first type" (*asymmetrische Umlagerung erster Art*) should be applied to cases such as the above, where a purely transient asymmetry is produced which disappears on removal of the optically active directing agent. On the other hand, the results of Leuchs, Mills and Bain, and others are designated "asymmetric transformations of the second type" (*zweiter Art*). Here, the initial material, originally racemic, appears partly or wholly as one optically active form *after* removal of the activating substance. Kuhn, however, recognises the possible existence of intermediate, border-line cases.

It will be recognised that the explanations advanced to account for the above phenomena make use of the basic conception of asymmetric induction. They are directly comparable to the case of the optically active *a*-ketonic esters examined by McKenzie and co-workers. Here, also, an optical

effect in solution is attributed to development of a transient, induced asymmetry: here, also, on removal of the inducing radical by saponification, an inactive *a*-ketonic acid is obtained. McKenzie and Mitchell [182] have attempted to resolve benzoylformic acid into antipodal forms by means of alkaloids: but no evidence could be obtained in this way to show that this acid can exist in enantiomorphous forms, stable or otherwise.

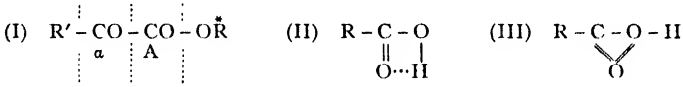
It is, of course, very doubtful how much stress may legitimately be laid on mere reversal of sign in passing from an optically active substance to one of its derivatives. Change of sign may quite possibly occur, with or without change of configuration, without involving the formation of a new centre of induced asymmetry, of opposite sign and dominating magnitude.* But the latter hypothesis is a stimulating one, and suggests many promising lines of investigation for the future: and it is difficult to avoid some such explanation in the case of most of the above-mentioned results.

* It has long been known, for example, that there is reversal of sign in passing from optically active lactic or glyceric acids to their sodium salts.

V

A NOTE ON THE CARBOXYLIC CARBONYL GROUP

ONE further point must be dealt with briefly before we leave the subject of asymmetric induction. In all the foregoing arguments, it has been tacitly assumed that the mutarotation of optically active *α*-ketonic esters is due to the *α*-carbonyl group (whether caused by solvation or by asymmetric induction), and not to the carbonyl group in the carboxyl radical, hereafter referred to as the A-carbonyl group.

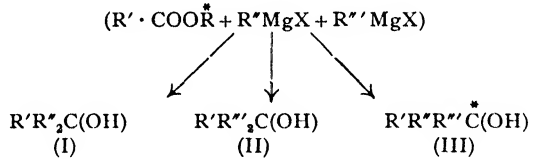


This view was suggested, in the first place, by the very markedly non-ketonic properties of the latter group. It does not, for example, form an oxime or a phenylhydrazone [246]: it is much less readily acted upon by reducing or Grignard reagents than a typical carbonyl group [247]: and its refractivity [248] and parachor are less than those of such a group. In addition, the system $O=\dot{C}-\dot{C}=O$ is usually regarded as a strong chromophore: but, whereas true diketones such as benzil, diacetyl, or camphorquinone are all markedly yellow in colour, this is not the case with *α*-ketonic esters.

No entirely satisfactory theory has been advanced to account for these anomalies. For various reasons, the coordinated ring structure (II) cannot be accepted: but the structure (III), suggested by Smedley [246], may be possible, while explanations on the basis of steric hindrance have also been suggested.

However this may be, it seems well established that the *a*-carbonyl group is markedly more reactive than the A-carbonyl group. Further, in the type of asymmetric synthesis studied by McKenzie, the *a-carbon atom* was readily converted into a new centre of asymmetry: while no such result has ever been realised with the A-*carbon atom*. These facts, coupled with the details quoted above, led to the assumption that it is the *a*-carbonyl group which is concerned in the observed mutarotation phenomena; and to the neglect of the A-carbonyl group until definite evidence concerning its stereochemical condition was forthcoming.

Several experiments [249] have been carried out by the present writer in an attempt to supply such evidence. Certain non-ketonic esters of the type $R' \cdot COO\overset{*}{R}$, where $\overset{*}{R}$ is an optically active alcoholic radical, were submitted to the simultaneous action of two different Grignard reagents, thus:



The final product should theoretically consist of a mixture of the three tertiary carbinols shown in the above scheme: and any optical activity displayed by the mixture, after elimination of the radical $\overset{*}{R}$, from traces of unattacked ester, must be due to an asymmetric synthesis of the unsymmetrical carbinol (III). Two different cases of this type were examined: in one, the product was optically inactive, while in the other only a slight degree of activity was

observed.* This result indicates that the conversion of the A-carbonyl group into a centre of fixed asymmetry has not proceeded to any significant extent. It does not, however, warrant the conclusion that this group is uninfluenced by the asymmetry of the radical $\overset{*}{\underset{\bullet}{R}}$. It may, perhaps, simply indicate that the Grignard reagents eliminated the group $-O\overset{*}{\underset{\bullet}{R}}$ (the directing system) before attacking the A-carbonyl grouping, thus:

$$R' \cdot COO\overset{*}{\underset{\bullet}{R}} + R''MgX \longrightarrow R' \cdot CO \cdot R'' + Mg\begin{matrix} O\overset{*}{\underset{\bullet}{R}} \\ X \end{matrix}$$

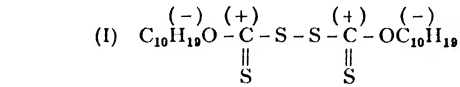
It has to be admitted that, while both the *a*- and A-carbonyl groups might theoretically exhibit induced asymmetry, the balance of evidence at present favours the *a*-group. Nevertheless, while leaving the question open, the writer would direct attention to four lines of argument, which focus attention on the A-carbonyl group:

(1) Lowry and Walker [161] have postulated induced asymmetry in a chromophoric group only if coupled sufficiently closely to a centre of fixed asymmetry. This is exactly parallel to the earlier suggestions of Tschugaeff, whose work on the rotatory dispersion of active xanthogenides led him to the conclusion that "a chromophore group situated in the neighbourhood of a centre of activity may produce anomalous dispersion within the limits of the visible spectrum, whilst if sufficiently remote from such a centre its influence on the shape of the dispersion

* In the cases examined, R', R'', and R''' were all *aromatic* radicals, in order to avoid risk of destroying the active centre by dehydrations of the type noted by Schlenk:

$$\begin{matrix} R' \\ R'' \end{matrix}\!\!>\!\overset{*}{\underset{\bullet}{C}}(OH) \cdot CH_3 \xrightarrow{(-H_2O)} \begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C=CH_2$$

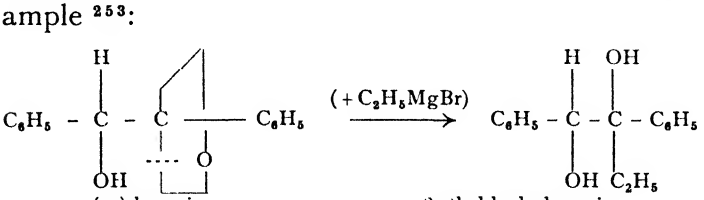
curve may be small or negligible [250]". Incidentally, it may be noted that Lowry and Walker suggest that the anomalous dispersion of Tschugaeff's (−)-menthyl dixanthogenide (I) may be due to the same basic cause as that of his (−)-menthyl (+)-camphor-β-sulphonate [251]. The dextrorotatory radical will possess *induced* asymmetry in the first case, and *fixed* asymmetry in the second case.



(I)

(2) Phillips' [202] suggested origin of complex rotatory dispersion in simple carboxylic esters postulates induced asymmetry in the A-group (see p. 100).

(3) Tiffeneau [252] has recorded certain observations suggesting that the directing influence of an optically active radical upon unsymmetrical addition reactions at a neighbouring carbonyl group diminishes as the distance between the two groups increases. He pictures the two links of the C = O double bond as being attacked differentially during an addition reaction, when in the neighbourhood of an optically active centre. When, for example, the C = O group is *directly* adjacent to such a centre, only *one* link is ruptured, and only one of the two possible diastereoisomerides is formed. For example [253]:

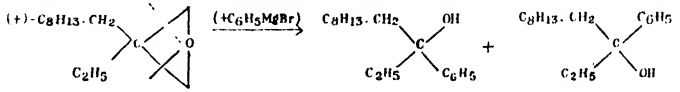


(+)-benzoin

β-ethyl-hydrobenzoin
(*unaccompanied by α-isomer*)

When, however, the C = O group is separated

from the active centre by one or more intervening inactive groups, both links of the double bond are ruptured when reaction occurs, but to different extents: both possible diastereoisomerides are therefor formed, one in excess over the other. For example [252]:*



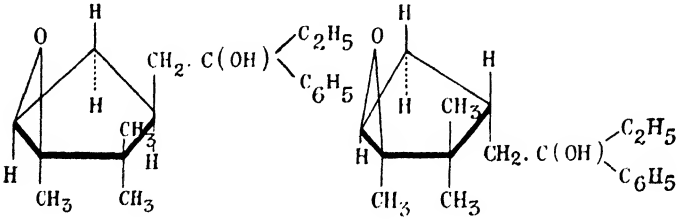
(Ketone derived from nitrile of (+)-campholenic acid.) — α-form (In excess) — β-form

(——— = principal point of rupture; . . . . . = subordinate point of rupture.)

The ratio of the two diastereoisomerides is supposed to approximate gradually to 1 : 1 as the number of groups between C = O and the active centre is increased.

Tiffeneau [252] applies the same simple conception to McKenzie's asymmetric syntheses from α-ketonic esters, dispensing with the idea of asymmetric induction. He explains the partial nature of such syn-

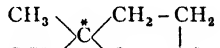
* The evidence for the simultaneous formation of both α- and β-isomers in this reaction is rather unsatisfactory. The liquid reaction product, on treatment with benzoyl peroxide, yielded *two* crystalline derivatives, which Tiffeneau assumed to be oxido-derivatives of the α- and β-isomers, respectively. But, even though only one form of the carbinol had originally been produced, the formation of the oxide ring introduces a possibility of *cis-trans*-isomerism which appears to have been overlooked.



(cis-) (trans-)

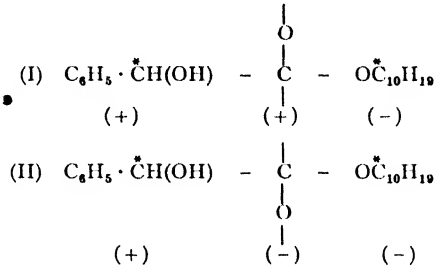
theses by the fact that the *a*-carbonyl group is not directly adjacent to the active directing radical, being separated from it by the intervening A-carbonyl group. The latter group, therefore, if influenced at all, would be expected to be more powerfully and completely "induced" than the *a*-group.

It is unfortunate that an early experiment by McKenzie [254], on asymmetric synthesis from (−)-menthyl lævulinate, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOC_{10}H_{19}(-)$, gave an inconclusive result: for the case is very interesting owing to the displacement of the ketonic group to the remote γ-position. The action of phenyl magnesium bromide yielded a slightly lævorotatory product: but its activity was presumably due to the formation of the asymmetric lactone

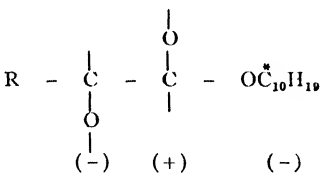


(4) Roger [255] has investigated the rotatory dispersion of the (−)-menthyl esters of (−)-, (+)-, and *r*-mandelic acids, and he suggests that the results may perhaps be complicated by the development of induced asymmetry in the A-carbonyl group which links the (−)-menthyl group to the mandelyl radical. He pictures the molecule of (−)-menthyl (−)-mandelate as possessing three centres of asymmetry, two "fixed", and one "induced", the latter assuming the same rotatory influence (*lævo*) as the other two. In the molecule of (−)-menthyl (+)-mandelate, however, the "centre of induced asymmetry is under the influence of two antagonistic centres and may be controlled by the fixed centre of most dominant character". In other words, the ester may have one of the two configurations shown below, probably

(I), "the superposition of the three partial rotations leading to anomalous dispersion".



Applying this idea to the rotatory dispersion of optically active *a*-ketonic esters, Roger and Ritchie[256] suggested that the observed complexity may be due to the presence in the molecule of one centre of fixed asymmetry and two centres of induced asymmetry. These need not all be of the same sign of rotation: the inductive effect may show some such alternation as the following:



This would be sufficient to account for the observed anomalous dispersion of (−)-menthyl *a*-naphthoylformate, which would, on this basis, constitute a complicated case of Tschugaeff's "*Intramolecular Anomaly*"[251].

VI

THE ROTATORY DISPERSION OF OPTICALLY ACTIVE *α*-KETONIC ESTERS

In the foregoing survey of asymmetric induction, the evidence considered has been of an almost purely chemical character: and it now remains to describe a series of experiments carried out by the writer, in which the problem was attacked from a physical point of view.

The line of attack was essentially simple. The rotatory dispersions of the two following series of optically active esters were examined:

(i) *Non-ketonic* (carboxylic) esters, of the type $R \cdot COO\overset{*}{R}$.

(ii) *α-Ketonic* esters, of the type $R \cdot CO \cdot COO\overset{*}{R}$.

If, now, we compare the rotatory dispersions of any corresponding pair of esters from the above groups, such as (−)-menthyl acetate ($CH_3 \cdot COOC_{10}H_{19}$) and (−)-menthyl pyruvate ($CH_3 \cdot CO \cdot COOC_{10}H_{19}$), any difference that may be observed must be attributed to the introduction of the *α*-carbonyl group into the molecule of the non-ketonic ester.

It was with no preconceived ideas on the ultimate significance of rotatory dispersion that this line of investigation was undertaken. Very widely divergent theories have been expressed on this phenomenon: and, in the absence of a universally acknowledged mechanism, it was felt inadvisable to theorise too boldly upon the basis of the observed experimental facts. Further, practical considerations limited these investigations to the range of wave-lengths covered

by the visible spectrum alone: whereas it was fully realised that absorption bands in the near ultra-violet may play a dominating rôle in determining the nature of the curve of rotatory dispersion, as the work of Kuhn, for example, has so brilliantly shown. Nevertheless, the line of attack outlined above provided some very suggestive results.

It was found that the two classes of esters differed markedly in their rotatory dispersions. The *non-ketonic* esters all displayed dispersions which could be represented by simple one-term Drude equations, over the whole range of wave-lengths employed (λ 4358-λ 6708). Examined by the graphical criteria of Lowry and Dickson [257], and of Bürki [258], they displayed no departure from simplicity: and application of the various criteria developed by Rupe and his co-workers [259] led to the same conclusion. Further, the dispersion curves were only slightly displaced by altering the conditions of solvent or temperature: and in all cases, the dispersion coefficient lay well above the limiting minimum value for simplicity. To sum up, *all the optically active non-ketonic esters displayed simple and normal dispersion.**

These results are in accordance with previous observations recorded in the same group. The dispersions of (−)-menthol and (−)-menthyl benzoate, for example, have been described as simple and normal [261]: and similar conclusions have been reached for the acetate [262] and other simple esters [263] of (−)-borneol. (−)-Borneol itself has been found to display simple and normal dispersion [264], though

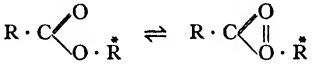
* With the possible exception of the β-naphthoates of (−)-menthol and (−)-borneol [260].

an earlier paper described the dispersion of (+)-borneol as complex [265].

These results are not surprising. The "characteristic diagram" [266] has been employed to predict the conditions under which certain compounds, which generally display simple and normal dispersion, might be expected to develop anomaly: and Frankland and Garner [267] point out that in the case of "menthol and its derivatives, owing to the limited range of accessible rotation values, the rotation-dispersion cannot readily be investigated under conditions in which the characteristic diagram indicates that it would be anomalous".

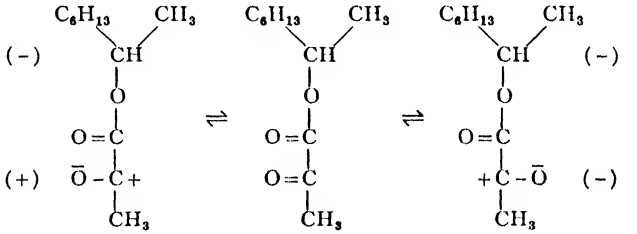
In the case, however, of various aliphatic esters of simple optically active secondary carbinols, the characteristic diagram indicated a more readily accessible region of potential anomaly than for the menthyl esters. By utilising conditions of solvent and temperature which depressed the rotatory power to the desired order of magnitude, visual anomaly was actually realised in the case, for example, of (+)-β-octyl acetate [268].

Now, the molecule of this ester contains only one classical asymmetric centre, and it has since been shown by Lowry and Richards [269] that β-octanol itself displays simple and normal dispersion. In order to account for the development of complexity in its esters, the hypothesis was advanced that two isodynamic forms are actually present in the apparently homogeneous ester, possibly of the following type [270]:



A few years ago, Phillips [202] suggested that the com-

plexity of dispersion might more readily be accounted for by assuming the existence of the equilibrium system already described on p. 100. A second labile centre of asymmetry is here produced in the esterified carboxyl group by the asymmetric inductive effect of the fixed asymmetric centre: and Phillips suggested that the existence of two partial rotations of opposite sign could be more easily explained in this way than by the mechanism previously postulated. Now, it will be seen that the hypothesis of asymmetric induction, as previously elaborated, requires the existence of an almost exactly parallel system in optically active α-ketonic esters.* For example, in (−)-β-octyl pyruvate, the following system would exist:



It might be expected that such a system would give rise to a rotatory dispersion governed by a Drude equation containing two terms of different dispersion parameters, and of the same or of opposite algebraic sign according to the precise conditions of equilibrium obtaining in the system. Now, although the complexity (if any) developed in menthyl and bornyl *non-ketonic* esters by the above mechanism could not be detected experimentally,

* For simplicity, the A-carbonyl group is neglected in this scheme. This is not altogether justified: as pointed out on p. 123, it is not unlikely to develop induced asymmetry as well as the α-carbonyl group.

the greater lability and reactivity of the *a*-carbonyl group rendered it not unlikely that this type of complexity might be more readily detected in *a-ketonic* menthyl and bornyl esters.

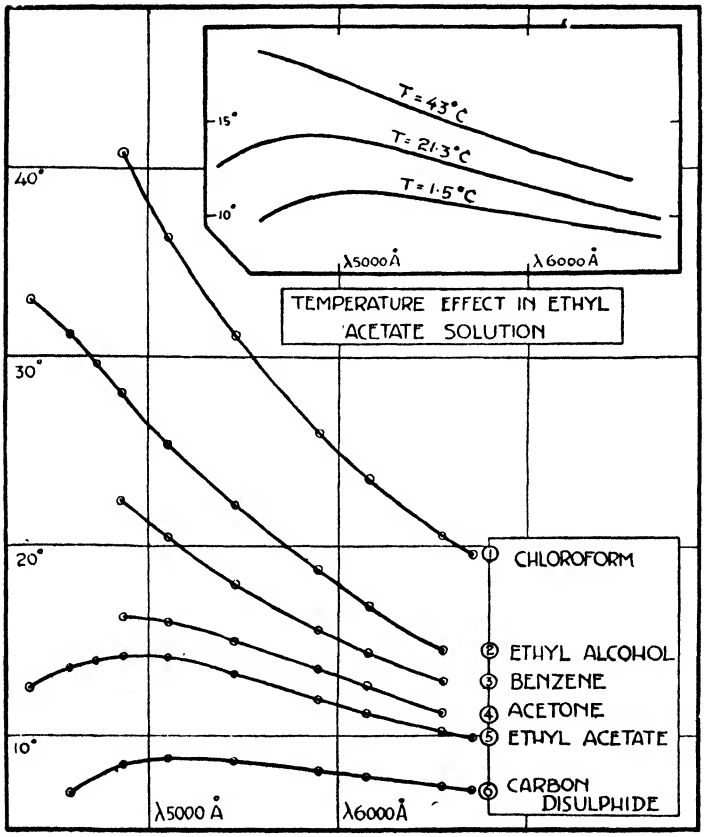


FIGURE II.

Rotatory Dispersion of (−)-Menthyl α-Naphthoylformate in various solvents. (Temperature approx. 20° C., unless otherwise indicated.)

The results obtained for these latter esters confirmed this expectation. In the first place, alteration of temperature, and, more particularly, of solvent,

now led to very marked displacement of the dispersion curves. This sensitiveness to solvent effect was reflected by a correspondingly greater variation in the Rupe criteria (λ_a and P.R.D.) in passing from solvent to solvent. The Bürki graphs were less regular than before: and in a few cases the dispersion coefficient fell below the limiting value for simplicity.

Investigation of the dispersions from the standpoint of the Drude equation, however, yielded the most definite and interesting results. Consider, for example, the rotatory dispersion of (−)-menthyl *a*-naphthoylformate in various solvents. Figure II shows the variation of [*a*] with λ for this ester, in six different solvents. It was found that in chloroform the dispersion obeyed a one-term equation: but on passing down the series of curves, the dispersion developed increasing degrees of complexity, until, in ethyl acetate and carbon disulphide solutions, visual anomaly was developed.

(−)-Menthyl *a*-naphthoylformate probably shows, under ideal conditions, phenomena which occur in all the other *a*-ketonic esters, though in these compounds the region of complex or anomalous dispersion is not so readily accessible to experiment. All displayed the same *type* of variation—strong solvent effect, especially in carbon disulphide,* and development of signs of complexity in passing down the series of curves. Figure III, for example, shows the dispersion curves for (−)-menthyl pyruvate. It may be noted that in this case, wherever complexity is

* The marked effect of this solvent is well known. Rule and Mitchell, for example, have found that the lævorotation of the (−)-β-octyl esters of certain substituted acetic acids is transformed into a dextrorotation by dissolving in carbon disulphide [271].

manifested, the curve of *observed* rotations (———) lies *above* the *theoretical* curve, calculated by means of a one-term Drude equation (.....): whereas in Figure II, the opposite is the case. This will be referred to later.

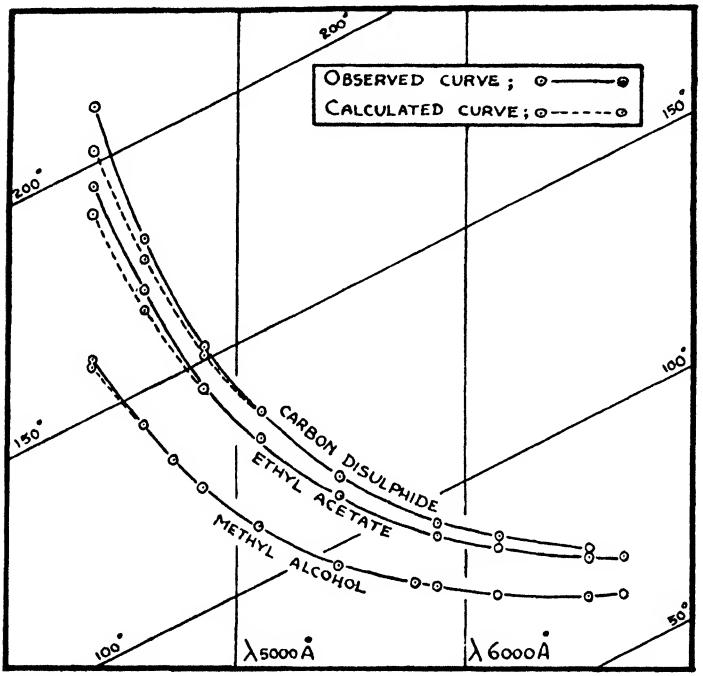


FIGURE III.

Rotatory Dispersion of (−)-Menthyl Pyruvate, showing Development of Complexity in certain Solvents.

The inset in Figure II shows, on a separate scale, the dispersion curves for (−)-menthyl *α*-naphthoyl-formate in ethyl acetate, at various temperatures: and it is worth noting that the development of visual anomaly with decrease in temperature is strikingly similar to the results obtained by Frank-

land and Garner with the butyl, octyl, and heptyl tartrates [267].

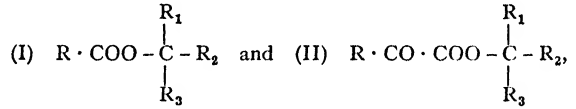
The "family" of curves shown in Figure II is, superficially, very similar to those recorded by Lowry and co-workers for ethyl [272] and methyl [273] tartrates, and for nicotine [274]. For these substances, the dispersion was found to vary from *normal but complex* to *complex and anomalous*, but could never be expressed by a one-term Drude equation: while in the case of (−)-menthyl α-naphthoylformate, the dispersion appears to vary continuously from *simple and normal* (in chloroform) to *complex and anomalous* (in carbon disulphide). The simplest interpretation of these results would appear to be that the two partial rotations, whose superposition generates the complex dispersion of the ester, arise in the "fixed" asymmetry of the (−)-menthyl radical and in the "induced" asymmetry of the α-carbonyl group, respectively. The former would not be expected to be markedly affected by change of solvent: but it will be readily accepted that such a sensitive effect as induced asymmetry would be greatly influenced by a change of solvent. It might, in fact, be almost totally inhibited in some solvents, in which case the rotatory dispersion would approximate, as in the case of the chloroform solution described above, to the simple and normal type displayed by non-ketonic (−)-menthyl esters. All the intermediate curves in the "family" are explicable on the very probable assumption that the equilibrium of the system described on p. 131 alters gradually and smoothly in changing from one solvent to the next.

It is possible, of course, to interpret the results in

other ways. Wood and Nicholas [162], for example, have put forward a general objection to the modern tendency "to seek a cause for a partial rotation of opposite sign in the molecule itself. . . . The necessity for seeking, either by isomeric change or by induced asymmetry, a centre giving rise to an opposite partial rotation is due to the non-recognition that a single asymmetric centre can give rise to two electronic components . . . which may contribute rotations of the same or opposite sign. . . . A theory which attaches importance to a hypothetical centre needs scrutiny" (compare p. 75). But so far this conception, though ingenious, must be regarded as a purely mathematical one. The conception of induced asymmetry, on the other hand, is more concrete and readily visualised, and finds a certain support in the fact that the dispersion equations of camphor and its derivatives are characterised by a low frequency term whose dispersion parameter corresponds very closely to the ketonic absorption band, with only a small systematic divergence [265]. It is quite reasonable, therefore, to assign this term to the partial rotation of the carbonyl centre of induced asymmetry: and it is submitted that the theory of asymmetric induction affords the simplest and most likely explanation of the way in which a second term, of different dispersive power, is introduced into the Drude equation in passing from a non-ketonic to an α-ketonic ester of this type.

It should be noted that the Drude equation referred to above is the simplified formula, so adequately sponsored by Lowry in his earlier researches, which is valid only in the region of complete transparency. Kuhn has developed a modified

form of this equation* which renders it valid also within the region covered by the active absorption band where the Cotton phenomenon has its origin: and by means of this formula he has expanded the integrated optical rotation of the molecule into a series of partial rotations connected with the individual constituent radicals or bands. A given substituent introduces a certain absorption frequency into the molecule: and though this, of itself, would produce no optical rotatory power, the band can become active by coupling with other bands already present in the molecule. Anisotropy of this type is known as *induced anisotropy*. As a natural corollary, it follows that such a band will influence the total rotatory power by inducing anisotropy in the bands of neighbouring substituent radicals, this effect being known as the *vicinal function* of the substituent. Thus, in considering esters such as



the vicinal function of the *a*-carbonyl group will play an important rôle in determining the change undergone by the curve of rotatory dispersion in passing from the non-ketonic (I) to the ketonic (II) compound.

It is obvious that the conceptions of asymmetric induction and vicinal function are very closely related, though the simplified mechanism suggested in the case of the optically active *a*-ketonic esters is

* $\phi = \sum_i \frac{a_i \lambda_i^2}{\lambda^2 - \lambda_i^2}$, where $\Sigma a_i = 0$. See also Addendum.

far less generalised and widely applicable than Kuhn's conception. The former is simply an attempt to provide a readily visualised working hypothesis to account for the writer's experimental results, and its tentative nature should once more be emphasised at this point.

It is a point worth noting that the optical behaviour of an active *a*-ketonic ester, $R' \cdot CO \cdot COO\dot{R}$, depends very markedly on whether the radical R' is aliphatic or aromatic. For example, the mutarotation of (−)-menthyl pyruvate (R' = methyl) is opposite in direction from that of all the other esters examined (where R' = phenyl, anisyl, or *a*-naphthyl). Correspondingly, the asymmetric syntheses effected by means of the pyruvates proceed in the opposite sense to those which start from the aromatic *a*-ketonic esters. Further, the change of specific rotatory power, with change of solvent, pursues the following sequence in (−)-menthyl pyruvate:

$$[\alpha]CS_2 > [\alpha]C_6H_6 > [\alpha]C_2H_5OH$$

For all the aromatic *a*-ketonic esters, however, this sequence is reversed:

$$[\alpha]CS_2 < [\alpha]C_6H_6 < [\alpha]C_2H_5OH$$

Finally, the dispersion curves of (−)-menthyl *a*-naphthoylformate (Figure II) suggest that a centre of induced asymmetry is present whose sense of rotation *opposes* that of the (−)-menthyl partial rotation: while the dispersion curves of (−)-menthyl pyruvate (Figure III) indicate that the centres have rotatory powers of the *same* sense.

These results are probably closely connected with the positive character of the methyl radical, and the

negative nature of the phenyl radical. Also, Kuhn [275] has pointed out that the optical rotation of mandelic acid is controlled by the marked anisotropy of the strong phenyl absorption band in the ultra-violet: whereas in the sugar acids, such as lactic acid, the controlling factor is the anisotropy of the carboxyl group, not of the aliphatic radical.

It will be seen that the evidence deduced from the dispersion figures differs from that deduced from purely chemical evidence, as regards the actual *sign of rotation* attributed to the *a*-carbonyl group, though both fields of evidence support the existence of such a centre in a state of induced asymmetry. At the present stage of our knowledge, it seems inadvisable to attempt to reconcile these results by making any fresh assumptions regarding the relation between configuration and sign of rotation: the whole conception is so largely a matter of speculation that the issue would merely be confused by such a procedure. We must simply accept the results as they stand, and leave the final unification until further definitely conclusive results become available.

ADDENDUM

ATTENTION must be drawn, in conclusion, to one or two papers published since the completion of the foregoing pages, which bear directly on the problems we have been considering.

Two recent papers by Lowry and co-workers lay considerable stress on the rôle of induced asymmetry in determining the rotatory dispersion of certain compounds. Lowry and Hudson [286] have measured the absorption, circular dichroism, and rotatory dispersion of Tschugaeff's bornyl and menthyl xanthates, and related compounds: and they provisionally attribute the absorption bands which determine the rotatory dispersion to the $-S \cdot CS-$, $>C=S$, and $-CS \cdot NR \cdot CS-$ groupings. "These chromophore groups do not usually exhibit optical activity; but they become optically active in the dissymmetric field of the bornyl or menthyl radical, and therefore exhibit the phenomenon of 'induced dissymmetry'." (Compare p. 124.)

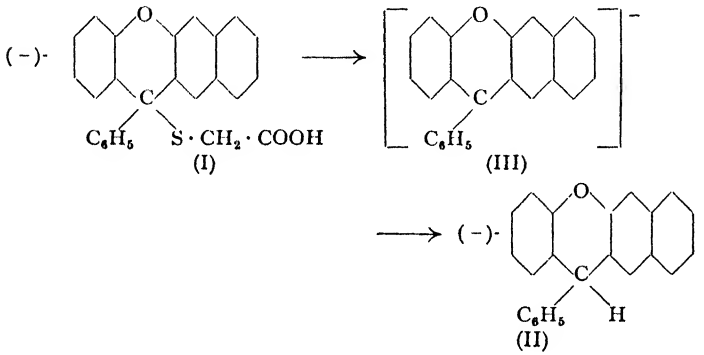
Lowry and Hudson developed a modified form of the equation employed by Kuhn and Braun to express the rotation produced by a single optically active absorption band*: and application of this equation, in a subsequent paper by Hudson, Wolfrom, and Lowry [287], led to interesting conclusions. The acetates of the open-chain, aldehydic μ-forms of glucose, galactose, and arabinose, were examined,

* For wave-lengths remote from the band concerned, both equations reduce to a form identical with Drude's equation, which, of course, is valid only in the region of complete transparency.

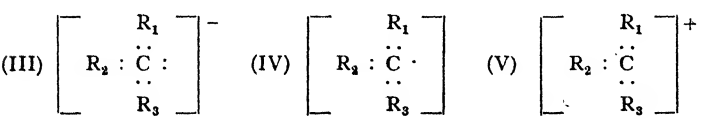
and it was found that here the ultra-violet absorption band at λ2900, due to the aldehydic (carbonyl) group, stood out as an isolated peak, free from the "overlapping" effect of contiguous bands which had complicated previous results obtained with the xanthates, and with derivatives of camphor [122] and α-azido-propionic acid. The partial rotation due to this band was deduced from its observed circular dichroism, by means of the above equation, and the difference between the curve thus plotted and the observed dispersion curve indicated the residual rotation due to the $>\dot{C}H \cdot O \cdot COCH_3$ groups. It was found that the rotatory dispersion of these acetylated μ-sugars included (i) a lævo partial rotation, governed by the characteristic "carbonyl" frequency, and (ii) a dextro partial rotation, with a characteristic frequency in the inaccessible Schumann region. This latter is obviously composite, and is regarded as the algebraic sum of a series of positive and negative terms with similar dispersion parameters, due to the fixed asymmetry of the $>\dot{C}H \cdot O \cdot COCH_3$ groups. For the glucose and galactose derivatives, this residual dextrorotation is small, producing only slight complexity of dispersion in the region of transparency: but for μ-arabinose tetra-acetate, the dispersion is simple, since here the Schumann terms virtually cancel out, and the dextro partial rotation disappears. The observed dispersion curve is almost identical with that given by Lowry and Hudson's equation: *and the whole of the observed lævorotation must therefore be attributed to the induced asymmetry of the terminal aldehydic group.*

On pp. 69-74, evidence was reviewed for the existence and retention of asymmetry in tricovalent

carbon ions. Recently, Wallis and Adams [288] have collected additional evidence bearing on this question. They treated (−)-12-phenyl-12-β-benzoxanthenethioglycollic acid (I) with a solution of sodium in liquid ammonia; and (−)-12-phenyl-β-benzoxanthene (II) was precipitated out from the sodium-triaryl-methyl complex (which contains an ionic C−Na bond) by treatment with ammonium bromide.



Since (II) was *optically active*, Wallis and Adams deduced that a negative ion (III), which they designate a "carbanion", is capable of existing in antipodal forms. Other experiments on analogous lines, however, led them to believe that a free radical (IV) and a carbonium ion (V) are incapable of maintaining their asymmetry, though in the case of the free radical a special mechanism may occasionally lead to the occurrence of a Walden inversion, without destruction of optical activity.



BIBLIOGRAPHY

NOTE: The existing literature on asymmetric synthesis, and more particularly on asymmetric induction, is very scattered, and few really comprehensive accounts exist. A survey of asymmetric synthesis as a whole was recently given by McKenzie (*Z. angew. Chem.*, 1932, **45**, 59): while a summary of asymmetric syntheses involving the use of enzymes will be found in Oppenheimer-Pincussen's *Die Methodik der Fermente* (Leipzig, 1929), v, 1308, and in Freudenberg's *Stereochemie* (Leipzig, 1933), vi, 921.

A short survey of asymmetric induction is included in Kortüm's "Neuere Forschungen über die optische Aktivität chemischer Moleküle" (*Samml. chem. u. chem.-tech. Vorträge*, x; Stuttgart, 1932). In addition, this publication gives an account of absolute asymmetric photosynthesis and the Cotton effect: and these subjects are also treated in detail in Kuhn and Freudenberg's "Drehung der Polarisationsebene des Lichtes" (Eucken-Wolf, *Hand- u. Jahrb. der chem. Physik*, iii; Leipzig, 1932), in Freudenberg's *Stereochemie* (Leipzig, 1932), iii, and in Mitchell's *The Cotton Effect and related Phenomena.* (London, 1933.)

The references in the text are as follows:

[1] BROWN and MORRIS, *J.C.S.*, 1893, **63**, 604.

[2] *Organic Chemistry* (Schmidt, English Edition, London, 1926), p. 432.

[3] NEUBERG, *Ber.*, 1900, **33**, 2243.

[4] HESS and WELTZIEN, *Ber.*, 1920, **53**, 119.

[5] PRINGSHEIM, *Ber.*, 1920, **53**, 1372.

[6] HESS, *Ber.* 1920, **53**, 1375.

[7] PASTEUR, *Compt. rend.*, 1851, **32**, 110: 1853, **36**, 26: 1858, **46**, 615: 1860, **51**, 298.

[8] FISCHER, *Ber.*, 1899, **32**, 3617.

[9] PFEFFER, *Bied. Zentr.*, 1896, **25**, 813: from Pringsheim's *Jahrb.*, 1895, **28**, 205, and *Bot. Zentr.*, 1896, **65**, 202.

[10] MCKENZIE and HARDEN, *J.C.S.*, 1903, **83**, 424.

[11] MARCKWALD and MCKENZIE, *Ber.*, 1899, **32**, 2130; see also MARCKWALD and PAUL, *Ber.*, 1905, **38**, 810: 1906, **39**, 3654.

[12] PASTEUR, *Bull. Soc. chim.*, 1884, **41**, 219.

[13] JAPP, *Nature*, 1898, **58**, 452.

[14] See also *Nature*, 1898, **58**, 495, 520, 545, 592, 616: 1899, **59**, 29, 30, 53, 54, 76, 101, 125.

[15] KUHN and BRAUN, *Naturwiss.*, 1929, **17**, 227.

[16] KUHN and KNOPF, *Naturwiss.*, 1930, **18**, 183; *Z. physikal. Chem.*, 1930, **7** (B), 292.

[17] MITCHELL, *J.C.S.*, 1930, 1829.

[18] Compare GOLDSCHMIDT, *Stereochemie* (Leipzig, 1933); EBEL, in Freudenberg's *Stereochemie* (Leipzig, 1932), iv, 581.

[19] Compare BREDIG and MANGOLD, *Z. angew. Chem.*, 1923, **36**, 456; EBEL, in Freudenberg's *Stereochemie* (Leipzig, 1932), iv, 584.

[20] FISCHER, *Ber.*, 1894, **27**, 3231.

[21] FISCHER, *Ber.*, 1889, **22**, 370: *Annalen*, 1892, **270**, 68; see also *Ber.*, 1904, **37**, 2486.

[22] FISCHER, *Ber.*, 1904, **37**, 2486.

[23] MCKENZIE and WREN, *J.C.S.*, 1910, **97**, 475.

[24] TIFFENAU, LÉVY, and KAYSER, *Compt. rend.*, 1933, **196**, 1407. Compare also: NICOLLE, *Bull. Soc. chim.*, 1925 (iv), **37**, 122; TIFFENEAU and LÉVY, *Bull. Soc. chim.*, 1927 (iv), **41**, 1351; MCKENZIE, LUIS, TIFFENEAU, and WEILL, *Bull. Soc. chim.*, 1929 (iv), **45**, 414; ROGER, *Helv. Chim. Acta*, 1929, **12**, 1060; ROGER, *Biochem. Z.*, 1931, **230**, 320; ROGER and MCKAY, *J.C.S.*, 1931, 2229.

[25] SMIRNOV, *Helv. Chim. Acta*, 1920, **3**, 177.

[26] JAEGER and BLUMENDAL, *Z. anorg. Chem.*, 1928, **175**, 161.

[27] LIFSCHITZ, *Z. physikal. Chem.*, 1923, **105**, 27.

[28] TSCHUGAEFF and SOKOLOFF, *Ber.*, 1907, **40**, 3464: 1909, **42**, 55.

[29] FISCHER, *Ber.*, 1901, **34**, 629.

[30] FISCHER and SLIMMER, *Sitzungsber. K. Akad. Wiss. Berlin*, 1902, **28**, 597; *Ber.*, 1903, **34**, 629.

[31] COHEN and WHITELEY, *J.C.S.*, 1901, **79**, 1305.

[32] KIPPING, *Proc. C.S.*, 1900, **16**, 226.

[33] HARTWALL, *Inaug. Dissert.*, Helsingfors, 1904.

[34] MARCKWALD, *Ber.*, 1904, **37**, 349.

[35] TIJMSTRA, BZ., *Ber.*, 1905, **38**, 2165.

[36] COHEN and PATTERSON, *Ber.*, 1904, **37**, 1012.

[37] MARCKWALD, *Ber.*, 1904, **37**, 1368.

[38] ERLENMEYER and LANDSBERGER, *Biochem. Z.*, 1914, **64**, 366.

[39] Compare, for example, GARDNER, PERKIN, and WATSON, *J.C.S.*, 1910, **97**, 1763; HILDITCH, *A Concise History of Chemistry* (London, 1911), p. 114; LEUCHS and WUTKE, *Ber.*, 1913, **46**, 2426; Annual Reports, 1915, **12**, 103; KOMATSU, *Mem. Coll. Sci. Kyoto*, 1916, i (10), 371; JAEGER, *Lectures on the Principle of Symmetry* (Amsterdam, 1917), 1st ed., p. 290; WEISS, *Monatsh.*, 1919, **40**, 391; STEWART, *Stereochemistry* (London, 1919), pp. 43-44; Annual Reports, 1920, **17**, 74; and various other references.

[40] MCKENZIE, *J.C.S.*, 1904, **85**, 1249.

[41] MCKENZIE and HUMPHRIES, *J.C.S.*, 1909, **95**, 1105.

[42] MCKENZIE, *J.C.S.*, 1905, **87**, 1373.

[43] MCKENZIE, *J.C.S.*, 1906, **89**, 365.

[44] MCKENZIE and WREN, *J.C.S.*, 1906, **89**, 688.

[45] MCKENZIE and MÜLLER, *J.C.S.*, 1909, **95**, 544.

[46] GRIGNARD, *Compt. rend.*, 1902, **135**, 627; *Ann. Chim. Phys.*, 1902 (vii), **27**, 548.

[47] MCKENZIE and RITCHIE, *Biochem. Z.*, 1931, **237**, 1.

[48] MCKENZIE and RITCHIE, *Biochem. Z.*, 1932, **250**, 376.

[49] MCKENZIE and RITCHIE, *Biochem. Z.*, 1931, **231**, 412.

[50] MCKENZIE and WREN, *J.C.S.*, 1907, **91**, 1215.

[51] SMILES, *J.C.S.*, 1905, **87**, 450.

[52] POPE and PEACHEY, *J.C.S.*, 1900, **77**, 1074.

[53] MENON and GUHA, *Ber.*, 1931, **64**, 544.

[54] WEISS, *Monatsh.*, 1919, **40**, 391.

[55] Compare, for example, WITTIG, *Stereochemie* (Leipzig, 1930), p. 40; GOLDSCHMIDT, *Stereochemie* (Leipzig, 1933), p. 29; also Annual Reports, 1920, **17**, 74.

[56] MCKENZIE and (Miss) S. T. WIDDOWS, *J.C.S.*, 1915, **107**, 702.

[57] DUNKEL, *Z. physikal. Chem.*, 1930, **10** (B), 434.

[58] KUHN, in Freudenberg's *Stereochemie* (Leipzig, 1933), vi, 803.

[59] (Miss) M. S. LESSLIE and TURNER, *J.C.S.*, 1930, 1758.

[60] (Miss) M. PEZOLD and SHRINER, *J. Amer. Chem. Soc.*, 1932, **54**, 4707.

[61] SHRINER and PARKER, *J. Amer. Chem. Soc.*, 1933, **55**, 766.

[62] BALCOM, *Inaug. Dissert.*, Heidelberg, 1905; BREDIG, *Biochem. Z.*, 1907, **6**, 303: *Z. angew. Chem.*, 1907, **20**, 310; BREDIG and BALCOM, *Ber.*, 1908, **41**, 740; BREDIG and FAJANS, *Ber.*, 1908, **41**, 752; FAJANS, *Z. physikal. Chem.*, 1910, **73**, 25: *Inaug. Dissert.*, Zürich, 1910; CREIGHTON, *Inaug. Dissert.*, Zürich, 1912: *Z. physikal. Chem.*, 1913, **81**, 543; BREDIG, *Verhandl. Naturw. Ver. Karlsruhe*, 1913, **25**; JOYNER, *Inaug. Dissert.*, Karlsruhe, 1913; BREDIG and JOYNER, *Z. Elektrochem.*, 1918, **24**, 285; PASTANOGOFF, *Z. physikal. Chem.*, 1924, **112**, 448; BREDIG and MINAEFF, *Festschrift Tech. Hochschule Karlsruhe*, 1925, **1**. (Compare, also, RONA and REUTER, *Biochem. Z.*, 1932, **249**, 455.)

[63] WUYTS, *Bull. Soc. chim. Belg.*, 1921, **30**, 30.

[64] WEGLER, *Annalen*, 1932, **498**, 62.

[65] DAKIN, *J. Physiol.*, 1904, **30**, 254.

[66] HERZOG and MEIER, *Z. physiol. Chem.*, 1909, **59**, 57.

[67] ABDERHALDEN and PRINGSHEIM, *Z. physiol. Chem.*, 1909, **59**, 249.

[68] CONDELLI, *Gazzetta*, 1921, **51** (II), 309.

[69] NEUBERG, WAGNER, and JACOBSOHN, *Biochem. Z.*, 1927, **188**, 227.

[70] WILLSTÄTTER, KUHN, and BAMANN, *Ber.*, 1928, **61**, 886.

[71] MITCHELL, *J.C.S.*, 1925, **127**, 208.

[72] BREDIG and FISKE, *Biochem. Z.*, 1912, **46**, 7; FISKE, *Inaug. Dissert.*, Zürich, 1911.

[73] BREDIG and MINAEFF, *Biochem. Z.*, 1932, **249**, 241.

[74] ROSENTHALER, *Biochem. Z.*, 1908, **14**, 238: 1909, **17**, 257: 1909, **19**, 186: 1910, **26**, 1: 1910, **26**, 7; *Fermentforsch.*, 1922, **5**, 334; *Arch. Pharm.*, 1911, **249**, 510.

[75] BREDIG and GERSTNER, *Biochem. Z.*, 1932, **250**, 414.

[76] BAMANN and LAEVERENZ, *Ber.*, 1930, **63**, 394.

[77] SHIBATA and TSUCHIDA, *Bull. Chem. Soc.*, Japan, 1929, **4**, 142.

[78] KRIEBLE, *J. Amer. Chem. Soc.*, 1913, **35**, 1643.

[79] KRIEBLE and WIELAND, *J. Amer. Chem. Soc.*, 1921, **43**, 164. Compare also ALBERS and HAMANN, *Biochem. Z.*, 1932, **255**, 44.

[80] (Miss) I. A. SMITH, *Ber.*, 1931, **64**, 427.

[81] DAKIN, *J. Biol. Chem.*, 1909, **5**, 213: 1922, **52**, 183.

[82] CHALLENGER and KLEIN, *J.C.S.*, 1929, 1644.

[83] JACOBSOHN, *Biochem. Z.*, 1931, **234**, 401.

[84] SUMIKI, *Bull. Jap. Soc. Ferment.*, 1928, **23**, 33.

[85] EMBDEN and SCHMIDT, *Biochem. Z.*, 1910, **29**, 423: 1912, **38**, 393.

[86] NEUBERG and LEWITE, *Biochem. Z.*, 1918, **91**, 257; NEUBERG and NORD, *Ber.*, 1919, **52**, 2237, 2248.

[87] NEUBERG and NORD, *Ber.*, 1919, **52**, 2248.

[88] FÄBER, NORD, and NEUBERG, *Biochem. Z.*, 1920, **112**, 313; NAGELSCHMIDT, *Biochem. Z.*, 1927, **186**, 317; NEUBERG and KOBEL, *Biochem. Z.*, 1925, **160**, 250.

[89] VEIBEL, *Biochem. Z.*, 1931, **239**, 456. Compare also LEVENE and WALTI, *J. Biol. Chem.*, 1932, **98**, 735.

[90] SANTOMAURO, *Biochem. Z.*, 1924, **151**, 48.

[91] SEN, *J. Indian Chem. Soc.*, 1924, **1**, 1.

[92] NEUBERG and HIRSCH, *Biochem. Z.*, 1921, **115**, 282: see also NEUBERG and OHLE, *Biochem. Z.*, 1922, **128**, 610.

[93] ROGER, *Biochem. Z.*, 1931, **230**, 320.

[94] For views on the structure of the ketol, see FAVORSKY, *Bull. Soc. chim.*, 1926 (iv), **39**, 216; KOTCHERGINE, *Bull. Soc. chim.*, 1928 (iv), **43**, 573; VON AUWERS and JORDAN, *Biochem. Z.*, 1924, **144**, 31; NEUBERG, *Biochem. Z.*, 1924, **144**, 44; NEUBERG and OHLE, *Biochem. Z.*, 1922, **127**, 327.

[95] NEUBERG and LIEBERMANN, *Biochem. Z.*, 1921, **121**, 311.

[96] BEHRENS and IVANOV, *Biochem. Z.*, 1926, **169**, 478.

[97] HIRSCH, *Biochem. Z.*, 1922, **131**, 178; NEUBERG and REINFURTH, *Biochem. Z.*, 1923, **143**, 553.

[98] NEUBERG and SIMON, *Biochem. Z.*, 1925, **156**, 374.

[99] NEUBERG and GORR, *Biochem. Z.*, 1924, **154**, 495; NEUBERG and ROSENTHAL, *Ber.*, 1924, **57**, 1436; NEUBERG and KOMAREWSKY, *Biochem. Z.*, 1927, **182**, 285; KITASATO, *Biochem. Z.*, 1928, **195**, 118; FALKENHAUSEN, *Biochem. Z.*, 1930, **219**, 241.

[100] NEUBERG, *Biochem. Z.*, 1913, **49**, 502: **51**, 484; *Der Zuckerumsatz der Zelle*, Jena, 1913; MEYERHOF, *Biochem. Z.*, 1925, **159**, 432; KUHN and HECKSCHER, *Z. physiol. Chem.*,

1926, **160**, 116; DAKIN and DUDLEY, *J. Biol. Chem.*, 1913, **14**, 425, 557.

[101] GORR and PERLMANN, *Biochem. Z.*, 1926, **174**, 433; NEUBERG and GORR, *Biochem. Z.*, 1925, **166**, 482; NEUBERG and KOBEL, *Biochem. Z.*, 1927, **182**, 470; NEUBERG and SIMON, *Biochem. Z.*, 1928, **200**, 468; WIDTMANN, *Biochem. Z.*, 1929, **216**, 475; compare also HAYASHI, *Biochem. Z.*, 1929, **206**, 223.

[102] NEUBERG and SIMON, *Biochem. Z.*, 1927, **186**, 331: 1928, **200**, 468; MAYER, *Biochem. Z.*, 1926, **174**, 420; BINDER-KOTRBA, *Biochem. Z.*, 1926, **174**, 443.

[103] NEUBERG and COLLATZ, *Biochem. Z.*, 1930, **225**, 242; (compare FISCHER and MORESCHI, *Ber.*, 1912, **45**, 2447); FUJISE, *Biochem. Z.*, 1931, **236**, 237, 241.

[104] JAEGER, *Optical Activity and High Temperature Measurements* (New York, 1930), p. 206.

[105] JAMIN, *Compt. rend.*, 1850, **31**, 696.

[106] BECQUEREL, *Compt. rend.*, 1899, **108**, 997.

[107] VAN 'T HOFF, *Die Lagerung der Atome in Raume*, 2nd ed., 1894, p. 30: 3rd ed., 1908, p. 8.

[108] BYK, *Z. physikal. Chem.*, 1904, **49**, 641; *Ber.*, 1904, **37**, 4696.

[109] PASTEUR, *Rev. scientifique*, 1884 (iii), **7**, 3.

[110] BOYD, *Inaug. Dissert.*, Heidelberg, 1896.

[111] MEYER, *Chem.-Ztg.*, 1904, **28**, 41: *Jahresb. der Schles. Ges. f. vaterl. Kultur*, 2nd. ed., 1903, p. 34.

[112] CURIE, *J. de Physique*, 1894 (iii), **3**, 409.

[113] See LANDOLT, *Optische Drehungsvermögen*, p. 111.

[114] GUYE and DROUGININE, *J. Chim. phys.*, 1909, **7**, 97: compare EULER, *Ark. Kemi. Mineral. Geol.*, 1911, **4**, 8.

[115] JAEGER, *Optical Activity and High Temperature Measurements* (New York, 1930), p. 76.

[116] HENLE and HAAKH, *Ber.*, 1908, **41**, 4261.

[117] BYK, *Ber.*, 1909, **42**, 141.

[118] PADOA, *Atti R. Accad. Lincei*, 1909 (v), **18**, ii, 390.

[119] PIRAK, *Biochem. Z.*, 1922, **130**, 76.

[120] ROSENTHAL, *Sitzungsber. Preuss. Akad. Wiss. Berlin*, 1908, **1**, 20.

[121] COTTON, *Ann. de Chim. et Phys.*, 1896 (vii), **8**, 347.

[122] KUHN and GORE, *Z. physikal. Chem.*, 1931, **12** (B), 392.

[123] COTTON, *J. Chim. Physique*, 1909, **7**, 81.

[124] FREUNDLER, *Ber.*, 1909, **42**, 233.

[125] BREDIG and MANGOLD, *Z. angew. Chem.*, 1923, **36**, 456.

[126] JAEGER and BERGER, *Rec. trav. chim.*, 1921, **40**, 153.

[127] BALY, HEILBRON, and BARKER, *J.C.S.*, 1921, **119**, 1025.

[128] ZOCHER and COPER, *Sitzungsber. Preuss. Akad. Wiss. Berlin*, 1925, 426: *Z. physikal. Chem.*, 1928, **132**, 313.

[129] KIPPING and POPE, *J.C.S.*, 1898, **73**, 606.

[130] OSTROMISSLENSKY, *Ber.*, 1908, **41**, 3035.

[131] JAEGER, *Optical Activity and High Temperature Measurements* (New York, 1930), p. 213.

[132] MILLS, *J.S.C.I.*, 1932, **51**, 750 *et seq.*

[133] READ and MCMATH, *J.C.S.*, 1925, **127**, 1583.

[134] KORTÜM, "Neuere Forschungen über die optische Aktivität chemischer Molekule" (*Samml. chem. u. chem.- tech. Vorträge*, Heft 10), Stuttgart, 1932.

[135] LE BEL, *Bull. Soc. chim.*, 1892 (iii), **8**, 613.

[136] A complete list of reference to Erlenmeyer's papers will be found in his obituary notice, *Ber.*, 1921, **54** (A), 107.

[137] DE JONG, *Chem. Zentr.*, 1919, III, 821: *Ber.*, 1922, **55**, 463; *Rec. trav. chim.*, 1930, **49**, 216; see also BILLMANN, *Ber.*, 1909, **42**, 182; LIEBERMANN, *Ber.*, 1909, **42**, 1027, 4659.

[138] ERLENMEYER, *Annalen*, 1904, **337**, 329; *Biochem. Z.*, 1911, **35**, 149: *Ber.*, 1905, **38**, 2562, 3496, 3499, 3891: 1906, **39**, 285, 1570: 1909, **42**, 2663.

[139] ALLEN, *Phil. Mag.*, 1920 (vi), **40**, 426.

[140] ERLENMEYER and HILGENDORFF, *Biochem. Z.*, 1911, **35**, 134.

[141] MCKENZIE and (Miss) A. G. MITCHELL, *Biochem. Z.*, 1930, **221**, 1.

[142] ERLENMEYER, HILGENDORFF, and LANDSBERGER, *Biochem. Z.*, 1914, **64**, 296.

[143] EBERT and KORTÜM, *Ber.*, 1931, **64**, 342.

[144] ERLENMEYER, *Biochem. Z.*, 1914, **66**, 509; ERLENMEYER, HILGENDORFF, and LANDSBERGER, *Biochem. Z.*, 1914, **64**, 382.

[145] WEDEKIND, *Ber.*, 1914, **47**, 3172.

[146] ERLENMEYER, *Biochem. Z.*, 1916, **74**, 137.

[147] ERLENMEYER, *Biochem. Z.*, 1919, **97**, 255.

[148] ERLENMEYER, *Biochem. Z.*, 1919, **97**, 261.

[149] E. and H. ERLENMEYER, *Biochem. Z.*, 1922, **133**, 52.

[150] H. ERLENMEYER, *Helv. Chim. Acta*, 1930, **13**, 731.

[151] PAULY, *Biochem. Z.*, 1914, **67**, 439.

[152] MCKENZIE, ROGER, and WILLS, *J.C.S.*, 1926, 782.

[153] MCKENZIE and DENNLER, *Ber.*, 1927, **60**, 220.

[154] KENYON, LIPSCOMB, and PHILLIPS, *J.C.S.*, 1930, 421.

[155] MYLES, Ph.D. Thesis, St. Andrews, 1931, p. 10, 13.

[156] WALDEN, *Naturwiss.*, 1925, **13**, 331.

[157] SMILES, *J.C.S.*, 1900, **77**, 1174.

[158] MCKENZIE, DREW, and MARTIN, *J.C.S.*, 1915, **107**, 26.

[159] JONES and WALLIS, *J. Amer. Chem. Soc.*, 1926, **48**, 169.

[160] WALLIS and NAGEL, *J. Amer. Chem. Soc.*, 1931, **53**, 2787. Compare also LEVENE, *Science*, 1927, **66**, 561, and ADAMS and WALLIS, *J. Amer. Chem. Soc.*, 1932, **54**, 4753.

[161] LOWRY and WALKER, *Nature*, 1924, **113**, 565: see also LOWRY, *Bull. Soc. chim.*, 1926 (iv), **39**, 203.

[162] WOOD and NICHOLAS, *J.C.S.*, 1928, 1671.

[163] TOLLOCZO, *Z. physikal. Chem.*, 1896, **20**, 412.

[164] GOLDSCHMIDT and COOPER, *Z. physikal. Chem.*, 1898, **26**, 714.

[165] COOPER, *J. Amer. Chem. Soc.*, 1900, **23**, 255.

[166] JONES, *Proc. Cambr. Phil. Soc.*, 1907, **14**, 27.

[167] SCHRÖER, *Ber.*, 1932, **65**, 966.

[168] KIPPING and POPE, *J.C.S.*, 1898, **73**, 606.

[169] KIPPING and POPE, *J.C.S.*, 1909, **95**, 103.

[170] MCKENZIE, *J.C.S.*, 1915, **107**, 440.

[171] MCKENZIE and (Miss) N. WALKER, *J.C.S.*, 1922, **121**, 349.

[172] MCKENZIE, PLENDERLEITH, and (Miss) N. WALKER, *J.C.S.*, 1923, **123**, 2875.

[173] WALDEN, *Ber.*, 1899, **32**, 1846.

[174] E. and O. WEDEKIND, *Ber.*, 1908, **41**, 456.

[175] BREDIG and BALCOM, *Ber.*, 1908, **41**, 740; BALCOM, *Inaug. Dissert.*, Heidelberg, 1905.

[176] FISCHER, *Ber.*, 1899, **32**, 3617; compare also CALDWELL, *Proc. Roy. Soc.*, 1904, **74**, 184.

[177] McKENZIE and WREN, *J.C.S.*, 1919, **115**, 602; McKENZIE and (Miss) I. A. SMITH, *J.C.S.*, 1922, **121**, 1348.

[178] McKENZIE and (Miss) I. A. SMITH, *J.C.S.*, 1923, **123**, 1962: 1924, **125**, 1582.

[179] M'KENZIE and (Miss) I. A. SMITH, *Ber.*, 1925, **58**, 894.

[180] (Miss) I. A. SMITH, *Ber.*, 1931, **64**, 1115.

[181] McKENZIE and (Miss) A. G. MITCHELL, *Biochem. Z.*, 1929, **208**, 456, 471.

[182] McKENZIE and (Miss) A. G. MITCHELL, *Biochem. Z.*, 1930, **224**, 242.

[183] (Miss) A. G. MITCHELL, Ph.D. Thesis, St. Andrews, 1930, p. 116.

[184] RITCHIE, Ph.D. Thesis, St. Andrews, 1932, p. 57.

[185] BAKER, INGOLD and THORPE, *J.C.S.*, 1924, **125**, 268.

[186] LAPWORTH and HANN, *J.C.S.*, 1902, **81**, 1491, 1499.

[187] RUPE and LENZINGER, *Annalen*, 1913, **398**, 372.

[188] HENRI and FROMAGEOT, *Bull. Soc. chim.*, 1925 (iv), **37**, 345; FROMAGEOT, *Bull. Soc. chim.*, 1926 (iv), **39**, 1207; FROMAGEOT and PERRAUD, *Biochem. Z.*, 1930, **223**, 213; GARINO, BALLETTO, THIERRY, and BECCHI, *Gazzetta*, 1930, **60**, 592. For a full summary of the literature, see I. St. Neuberg, *Biochem. Z.*, 1930, **215**, 165. Compare also SCHEIBLER and VOSS, *Ber.*, 1920, **93**, 389.

[189] BÖTTINGER, *Ber.*, 1877, **10**, 266.

[190] KENYON and PICKARD, *J.C.S.*, 1914, **105**, 1117.

[191] FORSTER, *J.C.S.*, 1901, **79**, 987: 1903, **83**, 98.

[192] BURGESS and LOWRY, *J.C.S.*, 1924, **125**, 2081.

[193] FAULKNER and LOWRY, *J.C.S.*, 1925, **127**, 1080.

[194] MILLS and GOTTS, *J.C.S.*, 1926, 3121.

[195] YUAN and ADAMS, *J. Amer. Chem. Soc.*, 1932, **54**, 2966, 4434.

[196] STOUGHTON and ADAMS, *J. Amer. Chem. Soc.*, 1932, **54**, 4426.

[197] MEISENHEIMER and BEISSWENGER, *Ber.*, 1932, **65**, 32.

[198] POPE and READ, *J.C.S.*, 1912, **101**, 759.

[199] READ and (Miss) C. C. STEELE, *J.C.S.*, 1927, 911.

[200] WREN, *J.C.S.*, 1909, **95**, 1585.

[201] WOLFROM, *J. Amer. Chem. Soc.*, 1930, **52**, 2464: 1931, **53**, 2275.

[202] PHILLIPS, *J.C.S.*, 1925, **127**, 2552.

[203] MEERWEIN and SÖNKE, *Ber.*, 1931, **64**, 2378.

[204] BAKER, *J.C.S.*, 1932, 2923; see also LOWRY, *J.S.C.I.*, 1932, **51**, 493.

[205] HEROLD and WOLF, *Z. physikal. Chem.*, 1931, **12** (B), 165.

[206] MEYER, *Ber.*, 1909, **42**, 1149: 1910, **43**, 157.

[207] BENNETT and WILLIS, *J.C.S.*, 1929, 262.

[208] RICHTER-ANSCHÜTZ, *Chemie der Kohlenstoffverbindungen*, 12th ed. (1928), i, 264.

[209] NORRIS and PRENTISS, *J. Amer. Chem. Soc.*, 1928, **50**, 3042.

[210] PHILLIPS, see [202]; HARRISON, KENYON, and PHILLIPS, *J.C.S.*, 1926, 2079; CLARKE, KENYON, and PHILLIPS, *J.C.S.*, 1927, 188.

[211] POPE and MANN, *J.C.S.*, 1922, **121**, 1052: 1924, **125**, 911.

[212] BERGMANN and TSCHUDNOWSKY, *Ber.*, 1932, **65**, 457.

[213] CHILES and NOYES, *J. Amer. Chem. Soc.*, 1922, **44**, 1798; see also *J. Amer. Chem. Soc.*, 1920, **42**, 2259: 1926, **48**, 2404.

[214] LEVENE and MIKESKA, *J. Biol. Chem.*, 1920, **45**, 593: 1922, **52**, 485: 1923, **55**, 795.

[215] WEISSBERGER and HAASE, *Ber.*, 1931, **64**, 2986; WEISSBERGER and BACH, *Ber.*, 1932, **65**, 265.

[216] RAY, *J. Amer. Chem. Soc.*, 1932, **54**, 295.

[217] SUGDEN, REED, and WILKINS, *J.C.S.*, 1925, **127**, 1525.

[218] LOWRY and OWEN, *J.C.S.*, 1926, 606.

[219] EASTMAN, *J. Amer. Chem. Soc.*, 1922, **44**, 438.

[220] LOWRY and CUTTER, *J.C.S.*, 1925, **127**, 609.

[221] KUHN and ALBRECHT, *Ber.*, 1927, **60**, 1297.

[222] SHRINER and YOUNG, *J. Amer. Chem. Soc.*, 1930, **52**, 3332.

[223] INGOLD and JESSOP, *J.C.S.*, 1929, 2357: 1930, 713.

[224] RITCHIE, unpublished observation.

[225] RITCHIE, Ph.D. Thesis, St. Andrews, 1932, p. 128.

[226] KUHN and ALBRECHT, *Annalen*, 1927, **455**, 272.

[227] CHRISTIE and KENNER, *J.C.S.*, 1922, **121**, 614; compare also *J.C.S.*, 1923, **123**, 614, 779, 1043, 1948.

[228] (Miss) M. S. LESSLIE and TURNER, *J.C.S.*, 1932, 2021.

[229] (Miss) M. S. LESSLIE and TURNER, *J.C.S.*, 1932, 2394.

[230] (Miss) F. R. SHAW and TURNER, *J.C.S.*, 1933, 135.

[231] BELL and ROBINSON, *J.C.S.*, 1927, 2234.

[232] TURNER, preliminary note in *J.S.C.I.*, 1932, **51**, 493-494.

[233] WAGNER-JAUREGG, in Freudenberg's *Stereochemie* (Leipzig, 1933), vi, 869.

[234] LEUCHS and WUTKE, *Ber.*, 1913, **46**, 2425.

[235] LEUCHS, *Ber.*, 1921, **54**, 830.

[236] GADAMER, *Arch. Pharm.*, 1920, **258**, 171.

[237] AHLBERG, *Racemisierungserscheinungen* (Lund, 1924), 21.

[238] WERNER, *Ber.*, 1912, **45**, 3061.

[239] MILLS and (Miss) A. M. BAIN, *J.C.S.*, 1910, **97**, 1866.

[240] POPE and PEACHEY, *Proc. C.S.*, 1900, **16**, 42, 116.

[241] MILLS and ELLIOTT, *J.C.S.*, 1928, 1291.

[242] READ and MCMATH, *J.C.S.*, 1925, **127**, 1572: 1926, 2183.

[243] PFEIFFER and QUEHL, *Ber.*, 1931, **64**, 2667.

[244] PFEIFFER and QUEHL, *Ber.*, 1932, **65**, 560; PFEIFFER and NAKATSUKA, *Ber.*, 1933, **66**, 415.

[245] KUHN, *Ber.*, 1932, **65**, 49.

[246] (Miss) I. SMEDLEY, *J.C.S.*, 1909, **95**, 231.

[247] MCKENZIE, *J.C.S.*, 1904, **85**, 1249.

[248] BRÜHL, *Ber.*, 1907, **40**, 896.

[249] ROGER and RITCHIE, *Biochem. Z.*, 1932, **253**, 241, 264; RITCHIE, Ph.D. Thesis, St. Andrews, 1932, p. 82, 129

[250] TSCHUGAEFF, *Trans. Faraday Soc.*, 1914, **10**, 73.

[251] TSCHUGAEFF, *Ber.*, 1911, **44**, 2023.

[252] TIFFENEAU and LÉVY, *Bull. Soc. chim.*, 1927 (iv), **41**, 1351; TIFFENEAU, LÉVY, and DITZ, *Compt. rend.*, 1931, **192**, 955; also, private communication to Prof. A. McKenzie.

[253] TIFFENEAU and LÉVY, *Bull. Soc. chim.*, 1927 (iv), **41**, 1351.

[254] MCKENZIE, *J.C.S.*, 1906, **89**, 382.

[255] ROGER, *J.C.S.*, 1932, 2168.

[256] ROGER and RITCHIE, *Biochem. Z.*, 1932, **253**, 239; RITCHIE, Ph.D. Thesis, St. Andrews, 1932, Part II.

[257] LOWRY and DICKSON, *J.C.S.*, 1913, **103**, 1067: *Trans. Faraday* Soc., 1914, **10**, 96.

[258] BÜRKI, *Helv. Chim. Acta*, 1924, **7**, 163.

[259] HAGENBACH, *Z. physikal. Chem.*, 1915, **89**, 570; RUPE, *Annalen*, 1915, **409**, 327; RUPE and KÄGI, *Annalen*, 1920, **420**, 33; RUPE, *Annalen*, 1922, **428**, 188; RUPE, HÉRITIER, and SCHAEFER, *Annalen*, 1927, **459**, 171; ROGER and MCKAY, *J.C.S.*, 1931, 2229.

[260] ROGER and RITCHIE, *Biochem. Z.*, 1932, **253**, 242, 244.

[261] LOWRY and ABRAM, *J.C.S.*, 1919, **115**, 300; RUPE, *Annalen*, 1915, **409**, 327.

[262] MOESVELD, *Proc. K. Akad. Wetensch. Amsterdam*, 1929, **32**, 344.

[263] KENYON and PRISTON, *J.C.S.*, 1925, **127**, 1472.

[264] ROGER and RITCHIE, *Biochem. Z.*, 1932, **253**, 243.

[265] LOWRY and CUTTER, *J.C.S.*, 1925, **127**, 604.

[266] ARMSTRONG and WALKER, *Proc. Roy. Soc.*, 1913 (A), **88**, 38; also many subsequent references by PATTERSON, PICKARD, and KENYON.

[267] FRANKLAND and GARNER, *J.C.S.*, 1919, **115**, 636.

[268] PICKARD and KENYON, *J.C.S.*, 1914, **105**, 830.

[269] LOWRY and RICHARDS, *J.C.S.*, 1924, **125**, 1593.

[270] PICKARD and KENYON, *J.C.S.*, 1914, **105**, 830; KENYON, D.Sc. Thesis, London, 1914.

[271] RULE and MITCHELL, *J.C.S.*, 1926, 3202.

[272] LOWRY and DICKSON, *J.C.S.*, 1915, **107**, 1173.

[273] LOWRY and ABRAM, *J.C.S.*, 1915, **107**, 1187.

[274] LOWRY and LLOYD, *J.C.S.*, 1929, 1771.

[275] KUHN, *Ber.*, 1930, **63**, 191; KUHN and FREUDENBERG, *Ber.*, 1931, **64**, 703.

[276] ROSENTHALER, *Z. Unters. Nahrungs- u. Genussmittel*, 1910, **20**, 448.

[277] AKAMATSU, *Biochem. Z.*, 1923, **142**, 188.

[278] KOTAKE, CHIKANO, and ISHIKARA, *Z. physiol. Chem.*, 1925, **143**, 218.

[279] Compare, for example, FISCHER, SÜS, and KLEBS, *Annalen*, 1931, **490**, 55; also FISCHER and SIEBEL, *Annalen*, 1932, **499**, 94.

[280] STOLL and WIEDEMANN, *Helv. Chim. Acta*, 1933, **16**, 307.

[281] WALLIS and DRIPPS, *J. Amer. Chem. Soc.*, 1933, **55**, 1701. Compare also JONES and WALLIS, *J. Amer. Chem. Soc.*, 1926, **48**, 169.

[282] CORBELLINI and PIZZI, *Atti Accad. Lincei*, 1932, **15**, 287.

[283] SEARLE and ADAMS, *J. Amer. Chem. Soc.*, 1933, **55**, 1649.

[284] VAVON and JAKUBOWICZ, *Compt. rend.*, 1933, **196**, 1614.

[285] WALLIS and MOYER, *J. Amer. Chem. Soc.*, 1933, **58**, 2598.

[286] LOWRY and HUDSON, *Proc. Roy. Soc.*, 1933 (A), **232**, 119.

[287] HUDSON, WOLFROM, and LOWRY, *J.C.S.*, 1933, 1179.

[288] WALLIS and ADAMS, *J. Amer. Chem. Soc.*, 1933, **55**, 3838.